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☐	L3	L2 and (met97 or methionine 97)	0
☐	L2	L1 near3 (mutati$ or substitu$ or delet$ or insert$)	19
☐	L1	Nurr1 or Nr4a2 or HzF-3 or RNR-1	270

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=> s Nurr1 or "HZF-3" or "RNR-1" or Nr4a2
L1 1261 NURR1 OR "HZF-3" OR "RNR-1" OR NR4A2

=> s l1 and (mutat? or substitu? or delet? or insert?)
L2 226 L1 AND (MUTAT? OR SUBSTITU? OR DELET? OR INSERT?)

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3 139 DUP REM L2 (87 DUPLICATES REMOVED)

=> s l3 and met?
L4 65 L3 AND MET?

=> d bib abs

L4 ANSWER 1 OF 65 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2007:277160 BIOSIS <<LOGINID::20070504>>
DN PREV200700266440
TI Regulation of GTP cyclohydrolase I expression by orphan receptor ***Nurr1*** in cell culture and in vivo.
AU Gil, Minchan; McKinney, Cushla; Lee, Mi Kyeong; Eells, Jeffrey B.; Phyillaier, Marcia A.; Nikodem, Vera M. [Reprint Author]
CS NIDDKD, Genet and Biochem Branch, NIH, Bldg 8-106,9000 Rockville Pike, Bethesda, MD 20892 USA
veran@intra.niddk.nih.gov
SO Journal of Neurochemistry, (APR 2007) Vol. 101, No. 1, pp. 142-150.
CODEN: JONRA9. ISSN: 0022-3042.
DT Article
LA English
ED Entered STN: 25 Apr 2007
Last Updated on STN: 25 Apr 2007
AB ***Nurr1*** is an orphan nuclear transcription factor essential for the terminal differentiation of dopamine (DA) neurons in the ventral midbrain (VM). To identify the ***Nurr1*** -target genes, we carried out microarray and quantitative real-time PCR analyses of ***Nurr1*** null and wild-type mice in VM at embryonic day (E) 12.5 and shortly after birth (P0). In addition to the absence of mRNAs of DA synthesizing enzymes, the guanosine 5'-triphosphate (GTP) cyclohydrolase I (GTPCH) was also substantially reduced in the VM of ***Nurr1*** -null mice. GTPCH is the first enzyme in the synthesis pathway of tetrahydrobiopterin (BH4), an essential cofactor for tyrosine hydroxylase in DA synthesis. In the mouse, ***Nurr1*** and GTPCH mRNA were first detected at E10.5, and GTPCH transcription paralleled that of ***Nurr1*** . Small interfering RNA targeted against ***Nurr1*** decreases GTPCH expression in MC3T3-E1 osteoblasts in cell culture. Cotransfection of ***Nurr1*** and the GTPCH-luciferase (luc) reporter increased the luc activity by about threefold in N2A cells. Additional analysis using 5'-***deletions*** and mutants revealed that ***Nurr1*** activates GTPCH transcription indirectly through the proximal promoter region, in the absence of the nerve growth factor-induced clone B (NGFI-B) responsive element-like sites, similarly, as recently reported for DA transporter regulation by ***Nurr1*** .

=> s l4 and PY<=2000
L5 6 L4 AND PY<=2000

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 6 ANSWERS - CONTINUE? Y/(N):y

L5 ANSWER 1 OF 6 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2001:97235 BIOSIS <<LOGINID::20070504>>
DN PREV200100097235
TI ***Nurr1*** exhibits cell type specific activation of the tyrosine hydroxylase gene.
AU Jensen, P. [Reprint author]; Reubish, D.; O'Malley, K.
CS Washington University School of Medicine, Saint Louis, MO, USA
SO Society for Neuroscience Abstracts, (***2000***) Vol. 26, No. 1-2, pp. Abstract No.-417.3. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 21 Feb 2001
Last Updated on STN: 15 Feb 2002
AB Knock out animals have revealed that ***Nurr1*** is a required factor for midbrain dopaminergic neurons. Although genetic data would argue against ***Nurr1*** having a direct role in the regulation of the

biosynthetic enzyme, tyrosine hydroxylase (TH), recent studies have suggested otherwise. To test this hypothesis further, ***Nurr1*** was cloned by RT-PCR, sequenced and placed downstream of the CMV promoter. This clone together with various rat TH promoter (rTHpr) constructs driving beta-gal were transfected into the dopaminergic cell lines MN9D and PC12, as well as the non-catecholaminergic neuroblastoma cell line, N2A. Co-expression of ***Nurr1*** had no effect on reporter gene activity using a variety of rTHpr constructs in either MN9D or PC12 cells. In contrast, in N2A cells ***Nurr1*** generated a thirteen-fold increase in rTHpr reporter gene expression. ***Deletion*** analysis suggested that the site activated by ***Nurr1*** in N2A cells is between 3.1 and 0.8kb upstream of the transcription initiation start site. Two potential ***Nurr1*** binding response elements (nbre), designated nbre-1 and nbre-2, are located within this region. Electro-mobility shift assays using oligonucleotides derived from nbre-1 and nbre-2 revealed unique banding patterns generated by N2A versus MN9D or PC12 nuclear proteins. These data suggest that N2A but not MN9D or PC12 cells express a factor capable of interacting with ***Nurr1*** thereby allowing it to activate the TH promoter. Currently we are testing whether associated transcription factors have a role in activating the TH promoter in conjunction with ***Nurr1*** . Thus, depending upon the cellular context ***Nurr1*** can directly activate the TH gene. Conceivably these same pathways are used in the development of dopaminergic cell types.

L5 ANSWER 2 OF 6 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2001:75812 BIOSIS <<LOGINID::20070504>>
DN PREV200100075812
TI The nuclear orphan receptor ***Nurr1*** binds and transactivates the promoter of the tyrosine hydroxylase gene but not that of the dopamine beta-hydroxylase gene.
AU Chung, S. [Reprint author]; Kim, C. H.; Andersson, T.; Isacson, O.; Kim, K. S.
CS McLean Hospital, Harvard Med. Sch., Belmont, MA, USA
SO Society for Neuroscience Abstracts, (***2000***) Vol. 26, No. 1-2, pp. Abstract No.-19.1. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 7 Feb 2001
Last Updated on STN: 12 Feb 2002
AB ***Nurr1*** , a member of the nuclear receptor superfamily, is essential for development, survival, and phenotypic specification of midbrain dopaminergic neurons. In this study, we tested the potential regulation of the tyrosine hydroxylase (TH) and dopamine b-hydroxylase (DBH) genes by ***Nurr1*** . To this end, a recombinant ***Nurr1*** protein was produced using in vitro transcription and translation reactions. This recombinant ***Nurr1*** was tested for its interaction with putative ***Nurr1*** -binding sites using the gel shift assays, competition assays, antibody co-incubation experiments, and DNase I footprinting analysis. Our results showed that ***Nurr1*** interact with putative ***Nurr1*** binding sites residing in the upstream promoter regions of the TH gene. Furthermore, transient cotransfection experiments were performed to address whether ***Nurr1*** can directly transactivate the TH and/or DBH promoter activities. Remarkably, our results indicate that ***Nurr1*** directly transactivates the transcriptional activity of the TH gene both in catecholaminergic and noncatecholaminergic cell lines. In a sharp contrast, ***Nurr1*** did not regulate the DBH promoter at all in any of the cell lines used. Taken together, our data suggest that ***Nurr1*** may differentially regulate the TH and DBH promoter activities. To identify functionally important ***Nurr1*** -responsive site(s), base ***substitutions*** were introduced into the putative ***Nurr1*** binding sites in the context of the TH-reporter gene construct. These site-directed ***mutational*** constructs as well as ***deletional*** constructs which contain different lengths of the TH promoter are being tested by transient cotransfection assays.

L5 ANSWER 3 OF 6 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2000:1061 BIOSIS <<LOGINID::20070504>>
DN PREV200000001061
TI Reduced ***Nurr1*** expression increases the vulnerability of mesencephalic dopamine neurons to MPTP-induced injury.
AU Le, Wei-dong [Reprint author]; Conneely, Orla M.; He, Y.; Jankovic, Joseph; Appel, Stanley H.
CS Department of Neurology, Baylor College of Medicine, 6501 Fannin Street, NB 302, Houston, TX, 77030, USA
SO Journal of Neurochemistry, (***Nov., 1999***) Vol. 73, No. 5, pp. 2218-2221. print.
CODEN: JONRA9. ISSN: 0022-3042.
DT Article
LA English
ED Entered STN: 23 Dec 1999
Last Updated on STN: 31 Dec 2001
AB ***Mutation*** in the ***Nurr1*** gene, a member of the nuclear receptor superfamily, causes selective agenesis of dopaminergic neurons in the midbrain of null mice. Homozygous ***Nurr1*** knockout mice (***Nurr1*** -/-) die 1 day after birth, but heterozygous mice (***Nurr1*** +/-) survive postnatally without obvious locomotor deficits. Although adult ***Nurr1*** +/- mice show significantly reduced ***Nurr1*** protein levels in the substantia nigra (SN), they display a normal range of tyrosine hydroxylase-positive neuron numbers in the SN and normal levels of dopamine in the striatum. The reduction in ***Nurr1*** expression in ***Nurr1*** +/- mice, however, confers increased vulnerability to the selective dopaminergic neurotoxin 1- ***methyl*** -4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) compared with wild-type (***Nurr1*** +/+) mice. This study suggests that ***Nurr1*** may play an important role in maintaining mature mesencephalic dopaminergic neuron function and that a defect in ***Nurr1*** may increase susceptibility to SN injury.

L5 ANSWER 4 OF 6 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 1999:527289 BIOSIS <<LOGINID::20070504>>
DN PREV199900527289
TI Identification of nuclear orphan receptors as regulators of expression of a neurotransmitter receptor gene.
AU Chew, Li-Jin; Huang, Fei; Boutin, Jean-Marie; Gallo, Vittorio [Reprint author]
CS Laboratory of Cellular and Molecular Neurophysiology, NICHD, NIH, 49 Convent Dr., Bldg. 49, Rm. 5A78, Bethesda, MD, 20892-4495, USA
SO Journal of Biological Chemistry, (***Oct. 8, 1999***) Vol. 274, No. 41, pp. 29366-29375. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DT Article
LA English
ED Entered STN: 10 Dec 1999
Last Updated on STN: 10 Dec 1999
AB Nuclear orphan receptors are known to be important mediators of neurogenesis, but the target genes of these transcription factors in the vertebrate nervous system remain largely undefined. We have previously shown that a 500-base pair fragment in the first intron of the GRIK5 gene, which encodes the kainate-preferring glutamate receptor subunit KA2, down-regulates gene expression. In our present studies, ***mutation*** of an 11-base pair element within this fragment resulted in a loss of nuclear protein binding and reverses negative regulation by the intron. Using yeast one-hybrid screening, we have identified intron-binding proteins from rat brain as COUP-TFI, EAR2, and ***NURR1*** . Gel shift studies with postnatal day 2 rat brain extract indicate the presence of COUP-TFs, EAR2, and ***NURR1*** in the DNA-protein complex. Competition assays with GRIK5-binding site ***mutations*** show that the recombinant clones exhibit differential binding characteristics and suggest that the DNA-protein complex from postnatal day 2 rat brain may consist primarily of EAR2. The DNA binding activity was also observed to be enriched in rat neural tissue and developmentally regulated. Co-transfection assays showed that recombinant nuclear orphan receptors function as transcriptional repressors in both CV1 cells and rat CG4 oligodendrocyte cells. Direct interaction of the orphan receptors with and relief of repression by TFIIB indicate likely role(s) in active and/or transrepression. Our findings are thus consistent with the notion that multiple nuclear orphan receptors can regulate the transcription of a widely expressed neurotransmitter receptor gene by binding a common element in an intron and directly modulating the activity of the transcription machinery.

L5 ANSWER 5 OF 6 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 1996:284131 BIOSIS <<LOGINID::20070504>>
DN PREV199699006487
TI Inhibition of Nur77/ ***Nurr1*** leads to inefficient clonal ***deletion*** of self-reactive T cells.
AU Zhou, Tong [Reprint author]; Cheng, Jianhua; Yang, Pingar; Wang, Zheng; Liu, Changdan; Su, Xiao; Bluethmann, Horst; Mountz, John D.
CS Dep. Med., Division Clinical Immunol. Rheumatol., The Univ. Alabama Birmingham, 701 South 19th Street, LHRB 473, Birmingham, AL 35294-0007, USA
SO Journal of Experimental Medicine, (***1996***) Vol. 183, No. 4, pp. 1879-1892.
CODEN: JEMEAV. ISSN: 0022-1007.
DT Article
LA English
ED Entered STN: 25 Jun 1996
Last Updated on STN: 25 Jun 1996
AB The Nur77/ ***Nurr1*** family of DNA binding proteins has been reported to be required for the signal transduction of CD3/T cell receptor (TCR)-mediated apoptosis in T cell hybridomas. To determine the role of this family of DNA-binding proteins in thymic clonal ***deletion*** , transgenic (Tg) mice bearing a dominant negative ***mutation*** were produced. The transgene consisted of a truncated Nur77 (DELTA-Nur77) gene encoding the DNA-binding domain of Nur77 ligated to a TCR-beta enhancer resulting in early expression in thymocytes. Apoptosis of CD4+CD8+ thymocytes mediated by CD3/TCR signaling was greatly inhibited in the DELTA-Nur77 Tg mice, compared with non-Tg littermates, after treatment with anti-CD3 or anti-TCR antibody in vivo and in vitro. Clonal ***deletion*** of self-reactive T cells was investigated in DELTA-Nur77-D-b/HY TCR-alpha/beta double Tg mice. There was a five-fold increase in the total number of thymocytes expressing self-reactive Db/HY TCR-alpha/beta in the DELTA-Nur77-TCR-alpha/beta double Tg male mice. Deficient clonal ***deletion*** of self-reactive thymocytes was demonstrated by a 10-fold increase in the CD4+CD8+ thymocytes that expressed Tg TCR-alpha/beta. There was an eight-fold increase in CD8+,

D-b/HY TCR-alpha/beta T cells in the lymph nodes (LN) of DELTA-Nur77-D-b/HY TCR-alpha/beta double Tg compared with D-b/HY TCR-alpha/beta Tg male mice. In spite of defective clonal ***deletion*** , the T cells expressing the Tg TCR were functionally anergic. In vivo analysis revealed increased activation and apoptosis of T cells associated with increased expression of Fas and Fas ligand in LN of DELTA-Nur77-D-b/HY TCR-alpha/beta double Tg male mice. These results indicate that inhibition of Nur77/ ***Nurr1*** DNA binding in T cells leads to inefficient thymic clonal ***deletion*** , but T cell tolerance is maintained by Fas-dependent clonal ***deletion*** in LN and spleen.

L5 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2000:707016 CAPLUS <<LOGINID::20070504>>
DN 133:291121
TI ***Method*** of affecting cholesterol catabolism using nuclear bile acid receptor, and screening ***method***
IN Forman, Barry M.; Wang, Haibo
PA City of Hope, USA
SO PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000057915	A1	20001005	WO 2000-US7836	20000324 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2368234	A1	20001005	CA 2000-2368234	20000324 <--
AU 2000039173	A	20001016	AU 2000-39173	20000324 <--
AU 780658	B2	20050407		
EP 1165135	A1	20020102	EP 2000-918345	20000324
EP 1165135	B1	20040901		
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JP 2004510682	T	20040408	JP 2000-607664	20000324
AT 274921	T	20040915	AT 2000-918345	20000324
EP 1473042	A1	20041103	EP 2004-75173	20000324
EP 1473042	B1	20060621		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
AT 330632	T	20060715	AT 2004-75173	20000324
PRAI US 1999-126334P	P	19990326		
EP 2000-918345	A3	20000324		
WO 2000-US7836	W	20000324		

AB ***Methods*** and compns. are provided for modulating genes which are controlled by the FXR orphan nuclear hormone receptor. In a preferred embodiment, the ***method*** involves modulation of the gene encoding Cyp7a, the enzyme responsible for a major pathway in the elimination of cholesterol. The invention also relates to ***methods*** for screening compds. which bind to and activate or inhibit the FXR nuclear hormone receptor.
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L1 1261 S NURR1 OR "HZF-3" OR "RNR-1" OR NR4A2
L2 226 S L1 AND (MUTAT? OR SUBSTITU? OR DELET? OR INSERT?)
L3 139 DUP REM L2 (87 DUPLICATES REMOVED)
L4 65 S L3 AND MET?
L5 6 S L4 AND PY<=2000

=> s l3 and PY<=2000
L6 18 L3 AND PY<=2000

=> s l6 not l5
L7 12 L6 NOT L5

=> d bib abs 1-
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L7 ANSWER 1 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2001:109438 BIOSIS <<LOGINID::20070504>>
DN PREV200100109438
TI Gene cascades in midbrain dopaminergic neurons: identification and genetic modification of transcription factors.
AU van Doorninck, J. H. [Reprint author]; Smidt, M. P.; Artola, A.; Burbach, J. P.
CS Utrecht University, Utrecht, Netherlands
SO Society for Neuroscience Abstracts, (***2000***) Vol. 26, No. 1-2, pp. Abstract No.-692.8. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience. ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 28 Feb 2001
Last Updated on STN: 15 Feb 2002
AB The substantia nigra (SN) and ventral tegmental area (VTA) contain dopaminergic cell groups which are involved in Parkinson disease and schizophrenia. We aim to identify genes which are important for the developmental specification and maintenance of these neurons. Several transcription factors are known to be expressed in these mesDA cells such as Lmx1b, ***Nurr1*** and Ptx3 (or Pitx3), all three of which are expressed both during development as well as in the adult stage. The nuclear orphan receptor ***Nurr1*** has been shown to induce TH expression in the SN and VTA. In contrast, the LIM homeodomain gene Lmx1b does not affect TH expression but is involved in a separate pathway. An Lmx1b null ***mutation*** leads to the absence of Pitx3 and the early loss of mesDA cells (Smidt et al, 2000). The role of the highly mesDA specific Pitx3 is not yet known and we follow two approaches to determine the role of Pitx3 in DA specific gene cascades. Firstly, we are screening for additional transcription factors of various classes in both embryonic and in adult stages of which the results will be presented. Secondly, we use several genetically modified mice (knock-outs and transgenics). Preliminary results suggest that mutant mice display morphological abnormalities in the SN and VTA. The above results show that distinct gene cascades exist in developing mesDA neurons. These can affect neurotransmitter synthesis as well as morphological maturation of the mesDA system and this has implications for neurological and psychotic disorders. Smidt et al, Nat Neurosci 2000 Apr;3(4):337-41

L7 ANSWER 2 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2001:97717 BIOSIS <<LOGINID::20070504>>
DN PREV200100097717
TI ***NURR1*** ***mutations*** in cases of schizophrenia and manic depressive disorder.
AU Carmine, A. [Reprint author]; Buervenich, S.; Arvidsson, M.; Xiang, F.; Zhang, Z.; Sydow, O.; Jonsson, E. G.; Sedvall, G. C.; Leonard, S.; Ross, R. G.; Freedman, R.; Chowdari, K. V.; Nimgaonkar, V. L.; Perlmann, T.; Anvret, M.; Olson, L.
CS Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden
SO Society for Neuroscience Abstracts, (***2000***) Vol. 26, No. 1-2, pp. Abstract No.-476.11. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience. ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 21 Feb 2001
Last Updated on STN: 15 Feb 2002
AB The development of mesencephalic dopamine neurons critically relies on the presence of functional Nur-related receptor 1 (***Nurr1***) protein, and mice lacking ***Nurr1*** fail to develop this clinically important group of neurons. The highly homologous ***NURR1*** (Formerly known as NOT) gene in humans therefore constitutes a good candidate gene for neurologic and psychiatric disorders.with involvement of the dopamine neuron system, e.g. Parkinson's disease, schizophrenia and manic depression. By automated sequencing of genomic DNA from patients and controls, we found two different missense ***mutations*** in exon 3 of ***NURR1*** . in two schizophrenic patients and another missense ***mutation*** in the same exon in an individual with manic depressive disorder. In an in-vitro assay all three ***mutations*** caused a similar reduction of transcriptional activity of ***NURR1*** dimers of about 30 to 40 percent. Neither of these three amino acid changes, nor any sequence change in coding regions whatsoever, were found in patients with Parkinson's disease or control DNA material of normal populations.

L7 ANSWER 3 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2001:64538 BIOSIS <<LOGINID::20070504>>
DN PREV200100064538
TI ***NURR1*** ***mutations*** in cases of schizophrenia and manic-depressive disorder.
AU Buervenich, Silvia; Carmine, Andrea; Arvidsson, Mariette; Xiang, Fengqing; Zhang, Zhiping; Sydow, Olof; Jonsson, Erik G.; Sedvall, Goran C.; Leonard, Sherry; Ross, Randal G.; Freedman, Robert; Chowdari, Kodavali V.; Nimgaonkar, Vishwajit L.; Perlmann, Thomas; Anvret, Maria; Olson, Lars [Reprint author]
CS Department of Neuroscience, Karolinska Institutet, 17177, Stockholm, Sweden
Lars.Olson@neuro.ki.se
SO American Journal of Medical Genetics, (***December 4, 2000***) Vol. 96, No. 6, pp. 808-813. print.
ISSN: 0148-7299.
DT Article
LA English

ED Entered STN: 31 Jan 2001
Last Updated on STN: 12 Feb 2002
AB Transgenic mice lacking the nuclear orphan transcription factor Nur-related receptor 1 (***Nurr1***) fail to develop mesencephalic dopamine neurons. There is a highly homologous ***NURR1*** gene in humans (formerly known as NOT) which therefore constitutes a good candidate gene for neurologic and psychiatric disorders with an involvement of the dopamine neuron system, such as Parkinson's disease, schizophrenia, and manic-depression. By direct sequencing of genomic DNA, we found two different missense ***mutations*** in the third exon of ***NURR1*** in two schizophrenic patients and another missense ***mutation*** in the same exon in an individual with manic-depressive disorder. All three ***mutations*** caused a similar reduction of in vitro transcriptional activity of ***NURR1*** dimers of about 30-40%. Neither of these amino acid changes, nor any sequence changes whatsoever, were found in patients with Parkinson's disease or control DNA material of normal populations.

L7 ANSWER 4 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2001:61310 BIOSIS <<LOGINID::20070504>>
DN PREV200100061310
TI Nuclear receptors regulate neuronal nitric oxide synthase gene expression in the central nervous system.
AU Wei, X. [Reprint author]; Sasaki, M.; Huang, H.; Dawson, V. L.; Dawson, T. M.
CS Johns Hopkins University School of Medicine, Baltimore, MD, USA
SO Society for Neuroscience Abstracts, (***2000***) Vol. 26, No. 1-2, pp. Abstract No.-49.6. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 31 Jan 2001
Last Updated on STN: 12 Feb 2002
AB Neuronal nitric oxide synthase (nNOS) gene is expressed in various regions of the brain. It participates in diverse biological processes such as neurotransmission, neuronal development and neuroendocrine regulation. Recently we cloned and characterized the mouse nNOS promoter. We found that its main promoter resides at exon 2 in primary cortical neurons, pituitary gonadotrope and neuroblastoma cells. There is one nuclear receptor response element within this proximal promoter to which steroidogenic factor 1 (SF-1) or SF-1 like protein can bind and regulate nNOS transcription. Within rat primary cortical cultures, ***deletion*** or ***mutation*** of the nuclear receptor binding site, and overexpression of dominant negative SF-1 construct or DAX-1 can significantly decrease KCl depolarization induced nNOS promoter activity. Overexpression of SF-1 increased basal and KCl stimulated promoter activity, and the increase was substantially larger than that of ***Nurr1*** , Nur77 and Coup-TFI. Since SF-1 may not be expressed in cortex, there could exist another novel SF-1 like nuclear receptor. In pituitary gonadotrope alphaT3-1 cells where SF-1 and nNOS are highly expressed, ***deletion*** or ***mutation*** of the nuclear receptor binding site, and dominant negative SF-1 or DAX-1 decreased nNOS basal promoter activity. Dominant negative SF-1 could significantly reduce endogenous nNOS protein expression. Overexpression of SF-1 or constitutively active VP16SF-1 increased nNOS promoter activity. Endogenous SF-1 can activate a minimal promoter with nuclear receptor binding sites, but not with ***mutated*** binding sites. The essential role of SF-1 or SF-1 like transcription factor regulation of nNOS was further confirmed by the GAL4 system.

L7 ANSWER 5 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 1999:424368 BIOSIS <<LOGINID::20070504>>
DN PREV199900424368
TI Differential expression of tyrosine hydroxylase in catecholaminergic neurons of neonatal wild-type and ***Nurr1*** -deficient mice.
AU Baffi, J. S.; Palkovits, M.; Castillo, S. O.; Mezey, E.; Nikodem, V. M. [Reprint author]
CS GBB/NIDDK/NIH, 10 Center Drive, Building 10, Room 8N317, Bethesda, MD, 20892-1766, USA
SO Neuroscience, (***July 15, 1999***) Vol. 93, No. 2, pp. 631-642. print.
CODEN: NRSCDN. ISSN: 0306-4522.
DT Article
LA English
ED Entered STN: 18 Oct 1999
Last Updated on STN: 18 Oct 1999
AB The orphan nuclear receptor ***Nurr1*** is a transcription factor that belongs to the steroid/thyroid hormone receptor superfamily and is expressed in many regions of the brain. To determine the physiological role of ***Nurr1*** , we previously generated mice with a null ***mutation*** in the ***Nurr1*** gene. ***Nurr1*** -null mice appear to develop normally but die within 12 h after birth. Subsequent analysis revealed the absence of neurotransmitter dopamine and tyrosine hydroxylase immunoreactivity in the central dopaminergic area of newborn pups. Herein, using in situ hybridization histochemistry, we show that ***Nurr1*** is expressed only in subset of catecholamine producing neurons (A2 partly, A8-A10 and A11 catecholaminergic cell groups), and is excluded from the norepinephrine producing neurons (A1, A2, A5-A6 catecholaminergic cell groups). ***Nurr1*** was not expressed in the dopamine synthesizing cell groups (A12-A16 catecholaminergic cell groups) of the diencephalon and the olfactory bulb. As previously shown and confirmed in this study, tyrosine hydroxylase immunoreactivity was absent in the substantia nigra and ventral tegmental area of ***Nurr1*** -deficient mice. However, the loss of ***Nurr1*** expression in A2 and A11 dopaminergic neurons did not affect their tyrosine hydroxylase immunoreactivity. This study begins to dissect cues necessary for understanding the complex regulation of the catecholaminergic biosynthetic pathway with regard to local, chemical and developmental changes in the brain.

L7 ANSWER 6 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 1998:306777 BIOSIS <<LOGINID::20070504>>
DN PREV199800306777
TI Dopamine biosynthesis is selectively abolished in substantia nigra/ventral tegmental tegmental area but not in hypothalamic neurons in mice with targeted disruption of the ***Nurr1*** gene.
AU Castillo, Susan O. [Reprint author]; Baffi, Judit S.; Palkovits, Miklos; Goldstein, David S.; Kopin, Irwin J.; Witta, Jassir [Reprint author]; Magnuson, Mark A.; Nikodem, Vera M. [Reprint author]
CS Natl. Inst. Diabetes Dig. Kidney Dis., Natl. Inst. Health, 10/8N317, 10 Center Drive, MSC 1766, Bethesda, MD 20892-1766, USA
SO Molecular and Cellular Neuroscience, (***May, 1998***) Vol. 11, No. 1-2, pp. 36-46. print.
CODEN: MOCNED. ISSN: 1044-7431.
DT Article
LA English
ED Entered STN: 15 Jul 1998
Last Updated on STN: 15 Jul 1998
AB To ascertain the function of an orphan nuclear receptor ***Nurr1*** , a transcription factor belonging to a large gene family that includes receptors for steroids, retinoids, and thyroid hormone, we generated ***Nurr1*** -null mice by homologous recombination. Mice, heterozygous for a single ***mutated*** ***Nurr1*** allele, appear normal, whereas mice homozygous for the null allele die within 24 h after birth. Dopamine (DA) was absent in the substantia nigra (SN) and ventral tegmental area (VTA) of ***Nurr1*** -null mice, consistent with absent tyrosine hydroxylase (TH), L-aromatic amino acid decarboxylase, and other DA neuron markers. TH immunoreactivity and mRNA expression in hypothalamic, olfactory, and lower brain stem regions were unaffected. L-Dihydroxyphenylalanine treatments, whether given to the pregnant dams or to the newborns, failed to rescue the ***Nurr1*** -null mice. We were unable to discern differences between null and wild-type mice in the cellularity, presence of neurons, or axonal projections to the SN and VTA. These findings provide evidence for a new mechanism of DA depletion in vivo and suggest a unique role for ***Nurr1*** in fetal development and/or postnatal survival.

L7 ANSWER 7 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 1998:256415 BIOSIS <<LOGINID::20070504>>
DN PREV199800256415
TI A divergent role of COOH-terminal domains in ***Nurr1*** and Nur77 transactivation.
AU Castillo, Susan O.; Xiao, Qianxun; Kostrouch, Zdenek; Dozin, Beatrice; Nikodem, Vera M. [Reprint author]
CS Natl. Inst. Health, Natl. Inst. Diabetes Dig. Kidney Dis., Genetics Biochem. Branch, Mechanisms Gene Regulation Sect., 10 Center Dr. MSC1766,
Bethesda, MD 20892-1766, USA
SO Gene Expression, (***1998***) Vol. 7, No. 1, pp. 1-12. print.
ISSN: 1052-2166.
DT Article
LA English
ED Entered STN: 9 Jun 1998
Last Updated on STN: 9 Jun 1998
AB Orphan nuclear receptors such as ***Nurr1*** and Nur77 have conserved amino acid sequences in the zinc finger DNA binding domains and similar COOH-terminal regions, but have no known ligands. These receptors can bind DNA sequences (response elements) as monomers and can also heterodimerize with the retinoid X receptor to activate transcription. We report here the identification and initial characterization of a novel COOH-terminal truncated isoform of ***Nurr1*** , Nurr1a. Internal splicing of ***Nurr1*** generates a frameshift such that a stop codon is prematurely encoded resulting in a naturally occurring COOH-terminal truncation. Embryonic and postnatal mouse brain showed both ***Nurr1*** and Nurr1a mRNAs expressed during development. To characterize essential COOH-terminal elements that may be ***deleted*** from Nurr1a and determine function in putative ligand binding, we created COOH-terminal ***deletion*** mutants. ***Nurr1*** , Nur77, and 3'-truncated mutants bind in gel mobility shift assays to the monomeric Nur77 response element (B1A-RE). However, in transient transfection assays, a truncation of as little as 15 ***Nurr1*** COOH-terminal amino acids diminished transcriptional activation of B1A-thymidine kinase-chloramphenicol acetyltransferase reporter. This result was not seen for a similar Nur77 ***deletion*** mutant, Nur77-586. Unlike full-length ***Nurr1*** and Nur77, transactivation by Nur77-586 was not augmented in response to the presence of retinoid-like receptor and 9-cis-retinoic acid. Thus, the interaction of putative ligand binding and transactivation for ***Nurr1*** and Nur77 may function differently.

L7 ANSWER 8 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 1997:366087 BIOSIS <<LOGINID::20070504>>
DN PREV199799658020
TI Rat ***nurr1*** is prominently expressed in perirhinal cortex, and differentially induced in the hippocampal dentate gyrus by electroconvulsive vs. kindled seizures.
AU Xing, Guoqiang [Reprint author]; Zhang, Lixin; Zhang, Lei; Heynen, Terri; Li, Xiu-Li; Smith, Mark A.; Weiss, Susan R. B.; Feldman, Arron N.; Detera-Wadleigh, Sevilla; Chuang, De-Maw; Post, Robert M.
CS Biol. Psychiatry Branch, Natl. Inst. Mental Health, Natl. Inst. Health, Build. 10, Room 3N212, 10 Center Drive, MSC 1272, Bethesda, MD 20892-1272, USA
SO Molecular Brain Research, (***1997***) Vol. 47, No. 1-2, pp. 251-261. CODEN: MBREE4. ISSN: 0169-328X.
DT Article
LA English
ED Entered STN: 25 Aug 1997
Last Updated on STN: 25 Aug 1997
AB We isolated a rat orphan nuclear hormone receptor from a brain cortex cDNA library. The sequence of the cDNA ***insert*** was 2154 bp with an open reading frame of 1794 bp encoding a putative protein of 598 amino acids and predicted molecular mass of 65 kDa. The deduced amino acid sequence showed a strong homology to the mouse ***nurr1*** and human NOT1 orphan nuclear hormone receptors of the NGFI-B/nur77/NAK1 gene subfamily. We refer to this rat clone as r- ***nurr1*** . Northern blot analysis showed that r- ***nurr1*** mRNA was highly expressed in the brain and moderately in the lung as a 4.0 kb transcript. A smaller transcript of 2.5 kb was also detected in the testes. The level of r- ***nurr1*** transcript in the heart, skeletal muscle, liver, kidney and spleen was marginal. In situ hybridization showed that r- ***nurr1*** mRNA was constitutively expressed in various regions of the CNS, particularly in the deeper layers (IV to VI) of the perirhinal cortex and area 2 of parietal cortex. We further evaluated the modulation of r- ***nurr1*** expression in CNS by an electroconvulsive seizure (ECS) and by an amygdala-kindled seizure. A single ECS administered via earclip electrodes induced a rapid and transient increase of r- ***nurr1*** mRNA in the granule cells of the dentate gyrus, being significant at 15 min after the seizure, maximal = 1 h and back to baseline at 4 h. The amygdala kindled seizure revealed a less robust and restricted ***nurr1*** induction in the CNS, as only two of the four kindled animals showed a unilateral induction of ***nurr1*** mRNA in the dentate gyrus. These results suggest that r- ***nurr1*** is an immediate-early gene that is differentially induced by ECS vs. kindled seizures. In addition, as r- ***nurr1*** is prominently expressed in the specific brain sites associated with memory acquisition and consolidation, it may play a role in memory processing.

L7 ANSWER 9 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 1997:85809 BIOSIS <<LOGINID::20070504>>
DN PREV199799377522
TI Neuroendocrine regulation of the hypothalamic pituitary adrenal axis by the ***nurr1*** /nur77 subfamily of nuclear receptors.
AU Murphy, Evelyn P.; Conneely, Orla M. [Reprint author]
CS Dep. Cell Biol., Baylor Coll. Med., One Baylor Plaza, Houston, TX 77030, USA
SO Molecular Endocrinology, (***1997***) Vol. 11, No. 1, pp. 39-47. CODEN: MOENEN. ISSN: 0888-8809.
DT Article
LA English
ED Entered STN: 26 Feb 1997
Last Updated on STN: 26 Feb 1997
AB The present study was designed to examine the role of the ***nurr1*** /nur77 subfamily of nuclear receptor transcription factors in the regulation of the hypothalamic/pituitary/adrenal axis at the neuroendocrine level. We demonstrate that this nuclear receptor subfamily can regulate the expression of the CRF and POMC genes by interacting with a specific cis-acting sequence in their proximal promoter regions. To examine the physiological significance of this response, we have focused on the POMC gene. We provide evidence that ***nurr1*** and nur77 are rapidly induced by CRF in primary pituitary cells and that this induction is mimicked by forskolin in an anterior pituitary cell line. Further, we demonstrate that both ***nurr1*** - and forskolin-dependent induction of a POMC-chloramphenicol acetyltransferase reporter gene are inhibited by ***mutation*** of the ***nurr1*** -binding site within the POMC promoter and that this site alone can confer cAMP responsiveness to a heterologous promoter. Finally, we provide evidence that the ***nurr1*** /nur77 response sequence is pivotal to both ***nurr1*** /nur77-dependent positive regulation and glucocorticoid receptor-dependent negative regulation of the POMC gene. These data strongly support the conclusion that the ***nurr1*** /nur77 subfamily plays an important coordinate neuroendocrine-regulatory role at all levels of the hypothalamic/pituitary/adrenal axis.

L7 ANSWER 10 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 1996:412423 BIOSIS <<LOGINID::20070504>>
DN PREV199699134779
TI Steroidogenic factor 1-dependent promoter activity of the human steroidogenic acute regulatory protein (StAR) gene.
AU Sugawara, Teruo; Holt, John A.; Kiriakidou, Marianthi; Strauss, Jerome F., III [Reprint author]
CS 778 Clin. Res. Build., 415 Curie Blvd., Philadelphia, PA 19104, USA
SO Biochemistry, (***1996***) Vol. 35, No. 28, pp. 9052-9059. CODEN: BICHAW. ISSN: 0006-2960.
DT Article
LA English
ED Entered STN: 10 Sep 1996
Last Updated on STN: 10 Sep 1996
AB Steroidogenic acute regulatory protein (STAR) is required for efficient adrenal cortical and gonadal but not trophoblast steroid hormone synthesis. StAR gene expression in gonadal cells is stimulated by tropic hormones acting through the intermediacy of cAMP. DNA sequence analysis of the human StAR gene promoter revealed two motifs resembling binding sites for steroidogenic factor 1 (SF-1), a member of the orphan nuclear receptor transcription factor family that controls expression of steroidogenic hydroxylases. The 5'-most sequence (distal site) is a consensus SF-1 binding site. The proximal site is a consensus estrogen receptor binding half-site. The StAR gene promoter is not active in BeWo choriocarcinoma cells, COS-1 cells, HeLa cells, or SK-OV-3 ovarian adenocarcinoma cells, all of which do not express significant levels of SF-1 mRNA. Introduction of SF-1 into these cells stimulated StAR promoter activity, particularly in response to cAMP. Two orphan nuclear transcription factors that bind to sequences similar to SF-1 sites, NGF1-B/Nur77 and ***RNR*** - ***1*** , did not support cAMP-stimulated StAR promoter activity in BeWo cells. ***Mutation*** of the distal putative SF-1 binding site reduced basal and cAMP-stimulated promoter activity in BeWo cells by 82% and 71%, respectively. ***Mutation*** of the proximal putative SF-1 binding site reduced basal and cAMP-stimulated promoter activity by 89% and 96%, respectively. ***Mutations*** in both sites reduced basal promoter activity to 7% of wild type promoter activity and cAMP-stimulated promoter activity to less than 5% of the wild type. ***Deletion*** analyses of promoter activity were consistent with the ***mutation*** studies. Electrophoretic mobility shift assays (EMSAs) demonstrated that the distal site binds to SF-1 expressed in COS-1 cells and to an SF-1-GST fusion protein with high affinity, but that the ***mutated*** distal sequence does not. An anti-SF-1 antibody ablated the characteristic SF-1-DNA complex with the distal sequence. The proximal site formed a number of protein-DNA complexes with COS-1 cell extracts, but appeared to have at best only very modest affinity for SF-1. Collectively, our findings demonstrate that SF-1 plays a key role in controlling the basal and cAMP-stimulated expression of the StAR gene. SF-1 can function at two distinct sites in the human StAR gene promoter, apparently by two different types of interaction, to control transcription.

L7 ANSWER 11 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 1996:63218 BIOSIS <<LOGINID::20070504>>
DN PREV199698635353
TI Oncogenic conversion of a novel orphan nuclear receptor by chromosome translocation.
AU Labelle, Yves; Zucman, Jessica; Stenman, Goran; Kindblom, Lars-Gunnar; Knight, Jennifer; Turc-Carel, Claude; Dockhorn-Dworniczak, Barbara; Mandahl, Nils; Desmaze, Chantal; Peter, Martine; Aurias, Alain; Delattre, Olivier; Thomas, Gilles [Reprint author]
CS INSERM U434 Genetique des Tumeurs, Inst. Curie, Section de Recherche, 26 rue d'Ulm, 75231 Paris Cedex 05, France
SO Human Molecular Genetics, (***1995***) Vol. 4, No. 12, pp. 2219-2226. ISSN: 0964-6906.
DT Article
LA English
OS DDBJ-X89894; EMBL-X89894; Genbank-X89894
ED Entered STN: 9 Feb 1996
Last Updated on STN: 13 Mar 1996
AB A recurrent t(9;22) (q22;q12) chromosome translocation has been described in extraskeletal myxoid chondrosarcoma (EMC). Fluorescent in situ hybridization experiments performed on one EMC tumour indicated that the chromosome 22 breakpoint occurred in the EWS gene. Northern blot analysis revealed an aberrant EWS transcript which was cloned by a modified RT-PCR procedure. This transcript consists of an in-frame fusion of the 5' end of EWS to a previously unidentified gene, which was named TEC. This fusion transcript was detected in six of eight EMC studied, and three different junction types between the two genes were found. In all junction types, the putative translation product contained the amino-terminal transactivation domain of EWS linked to the entire TEC protein. Homology analysis showed that the predicted TEC protein contains a DNA-binding domain characteristic of nuclear receptors. The highest identity scores were observed with the ***NURR1*** family of orphan nuclear receptors. These receptors are involved in the control of cell proliferation and differentiation by modulating the response to growth factors and retinoic acid. This work provides, after the PML/RAR-alpha gene fusion, the second example of the oncogenic conversion of a nuclear receptor and the first example involving the orphan subfamily. Analysis of the disturbance induced by the EWS/TEC protein in the nuclear receptor network and their target genes may lead to new approaches for EMC treatment.

L7 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1999:468603 CAPLUS <<LOGINID::20070504>>
DN 131:98493
TI Replication defective herpes virus (HSV-2) vector and its use in the

treatment of neurological disorders
IN Aurelian, Laure; Calton, Gary; Kulka, Michael
PA Aurx, Inc., USA
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9936513	A1	19990722	WO 1999-US921	19990115 <--
W: AU, CA, JP, KR				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9922313	A	19990802	AU 1999-22313	19990115 <--
PRAI US 1998-9531	A	19980120		
WO 1999-US921	W	19990115		

AB The invention relates to a replication defective herpes virus (HSV-2) which has been sufficiently ***deleted*** in the gene (ICP10) coding for the large subunit of ribonucleotide reductase (RR1) to render the produced proteins defective in their function. ICP10 codes for RR1 and a serine/threonine protein kinase, which is required for the prodn. of the viral IE proteins ICP4 and ICP27 that regulate the expression of all other HSV genes and RR1. Since the virus does not have ribonucleotide reductase activity nor protein kinase activity, the virus cannot replicate itself nor express other viral genes, and the sequences which code for the small RR subunit (RR2) may be ***deleted*** in order to provide addnl. space for foreign genes. The replication defective virus may have a therapeutic gene sequence ***inserted*** in the place of these ***deleted*** or partially ***deleted*** genes. The ***insertion*** of a gene for a neurotrophic factor may be driven by an appropriate promoter and may be used in the treatment of neurol. disorders such as Parkinson's disease, Alzheimer's disease, diabetic neuropathy, and neuropathic pain resulting from nerve injury.
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NEWS 17 FEB 26 CAS Registry Number crossover limit increased from 10,000 to 300,000 in multiple databases
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NEWS 21 MAR 22 LWPI reloaded
NEWS 22 MAR 30 RDISCLOSURE reloaded with enhancements
NEWS 23 APR 02 JICST-EPLUS removed from database clusters and STN
NEWS 24 APR 30 GENBANK reloaded and enhanced with Genome Project ID field
NEWS 25 APR 30 CHEMCATS enhanced with 1.2 million new records
NEWS 26 APR 30 CA/CAplus enhanced with 1870-1889 U.S. patent records
NEWS 27 APR 30 INPADOC replaced by INPADOCDB on STN
NEWS 28 MAY 01 New CAS web site launched
NEWS 29 MAY 08 CA/CAplus Indian patent publication number format defined

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L2 ANSWER 1 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2007:199211 BIOSIS <<LOGINID::20070510>>
DN PREV200700205387

TI The NR4A nuclear receptor family in eosinophils.
AU Hashida, Ryoichi [Reprint Author]; Ohkura, Naganari; Saito, Hirohisa; Tsujimoto, Gozoh
CS Genox Res Inc, Tokyo 1128088, Japan
hashiryo@mail1.accsnet.ne.jp
SO Journal of Human Genetics, (JAN 2007) Vol. 52, No. 1, pp. 13-20.
ISSN: 1434-5161. E-ISSN: 1435-232X.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 21 Mar 2007
Last Updated on STN: 21 Mar 2007
AB It is well-known that many members of the family of nuclear receptors have been implicated in human diseases, and metabolic disorders in particular. The NR4A nuclear receptor family consists of three members, Nur77, Nurr1, and NOR1. All of these are orphan receptors, and Nur77 and NOR1 exert possible pathological roles in immune diseases through the modulation of leukocyte functions. CD30 stimulation, which induces eosinophil-specific apoptosis, markedly enhances expression of Nur77 and NOR1 in eosinophils. This suggests the possibility of pharmacological modulation of Nur77- or NOR1-specific apoptotic pathways via receptor-dependent transactivation. In this review, we discuss treatment of allergic diseases by low molecular weight compounds acting through the NR4A receptor family to cause eosinophil apoptosis. NR4A nuclear receptor genes were selected following comprehensive analysis of differentially expressed genes in eosinophils of atopic dermatitis patients compared with healthy volunteers.

L2 ANSWER 2 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2006:537497 BIOSIS <<LOGINID::20070510>>
DN PREV200600547019
TI Mutant NURR1 gene in Parkinson's disease.
AU Anonymous; Le, Wei-Dong [Inventor]; Vassilatis, Demetrios K. [Inventor]
CS Houston, TX USA
ASSIGNEE: Baylor College of Medicine
PI US 07037657 20060502
SO Official Gazette of the United States Patent and Trademark Office Patents, (MAY 2 2006)
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 18 Oct 2006
Last Updated on STN: 18 Oct 2006
AB The identification of ***mutations*** in ***NURR1*** provides molecular tools for the development of diagnostic, prophylactic and therapeutic agents for Parkinson's Disease. In specific embodiments, two point mutations are identified in exon 1 of the NURR1 gene in 10/107 (9.3%) cases of familial Parkinson's disease (PD). The ***mutations*** reduce ***NURR1*** gene expression (mRNA and protein levels) by 87-95% and decrease tyrosine hydroxylase (a rate-limited dopamine synthesis enzyme) gene expression in vitro. It is also demonstrated that in vivo NURR1 mRNA levels in the lymphocytes from the PD patients with the exon 1 mutation are reduced by 68-84%, and in over 50% sporadic PD patients the NURR1 mRNA levels in lymphocytes are significantly reduced. A homozygous polymorphism is identified in intron 6 of NURR1 that correlates with the presence of Parkinson's disease. A splicing variant in NURR1 exon 5 is identified.

L2 ANSWER 3 OF 35 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 2006377181 EMBASE <<LOGINID::20070510>>
TI Translated ***mutation*** in the ***Nurr1*** gene as a cause for Parkinson's disease.
AU Grimes D.A.; Han F.; Panisset M.; Racacho L.; Xiao F.; Zou R.; Westaff K.; Bulman D.E.
CS Dr. D.A. Grimes, Ottawa Hospital, 1053 Carling Avenue, Ottawa, ON K1Y 4E9,
Canada. dagrimes@ottawahospital.on.ca
SO Movement Disorders, (2006) Vol. 21, No. 7, pp. 906-909. .
Refs: 19
ISSN: 0885-3185 E-ISSN: 1531-8257 CODEN: MOVDEA
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
022 Human Genetics
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
ED Entered STN: 25 Aug 2006
Last Updated on STN: 25 Aug 2006
AB Multiple genes have been now identified as causing Parkinson's disease (PD). In 2003, two mutations were identified in exon 1 of the Nurr1 gene in 10 of 107 individuals with familial PD. To date, investigators have only focused on screening for these known ***mutations*** of the ***Nurr1*** gene. All individuals were recruited from two Parkinson's disease clinics in Canada. Following PCR amplification of each exon of the Nurr1 gene, samples underwent denaturing high-performance liquid chromatography (DHPLC) analysis. Ten individuals also underwent direct sequencing as well as any samples where variants were identified. The Nurr1 gene was evaluated for 202 PD individuals, 37% of whom had at least one relative with PD and 100 control non-PD individuals. Using DHPLC and direct sequencing, we did not detect any sequence variants in exon 1. Variants in amplicon 6 were seen and direct sequencing confirmed a known NI6P polymorphism in intron 6. Novel polymorphisms were also identified in exon 3 and intron 5. A novel mutation was identified in exon 3 in one nonfamilial PD individual. This heterozygous C-to-G transversion resulted in a serine-to-cysteine substitution and was not identified in any of the other 602 chromosomes screened. ***Mutations*** in the ***Nurr1*** gene in our large cohort of familial and sporadic PD individuals are rare. The novel mutation in exon 3 is predicted to affect phosphorylation and functional studies to assess this are underway. This is the first coding ***mutation*** identified in the ***Nurr1*** gene for Parkinson's disease. .COPYRGT. 2006 Movement Disorder Society.

L2 ANSWER 4 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
DUPLICATE 1
AN 2006:647867 BIOSIS <<LOGINID::20070510>>
DN PREV200600636953
TI Characterization of the Nurr1 ligand-binding domain co-activator interaction surface.
AU Volakakis, Nikolaos; Malewicz, Michal; Kadkhodai, Banafsheh; Perlmann, Thomas [Reprint Author]; Benoit, Gerard
CS Karolinska Inst, Dept Cell and Mol Biol, S-17177 Stockholm, Sweden
thomas.perlmann@licr.ki.se
SO Journal of Molecular Endocrinology, (OCT 2006) Vol. 37, No. 2, pp. 317-326.
CODEN: JMLEEI. ISSN: 0952-5041.
DT Article
LA English
ED Entered STN: 22 Nov 2006
Last Updated on STN: 22 Nov 2006
AB The recently solved crystal structure of the orphan nuclear receptor (NR) Nurr1 ligand-binding domain (LBD) showed that Nurr1 lacks a cavity for ligand binding and a canonical NR co-activator-binding site. Computer modeling of the Nurr1 LBD structure identified a hydrophobic region on the surface of the Nurr1 LBD that was positioned on the opposite side from the classical co-activator-binding site. Site-directed mutagenesis demonstrated that this region is critical for the activity of the Nurr1 LBD. Most mutations introduced in this region reduced or abolished transcriptional activity of the ***Nurr1*** LBD, but ***mutation*** at lysine (K577) resulted in a drastically increased activity. Moreover, the activity of the Nurr1 LBD was shown to correlate with a propensity for proteasome-dependent degradation revealing a close association between activity and Nurr1 protein turnover. These data provide novel insights into the mechanisms of transcription via the Nurr1 LBD and identify an alternative co-activator-binding surface that is unique to the NR4A family of NRs.

L2 ANSWER 5 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2006:270958 BIOSIS <<LOGINID::20070510>>
DN PREV200600273859
TI Phenotype/genotype correlations in Parkinson's disease.
AU Brice, Alexis [Reprint Author]; Lohmann, Ebba; Ibanez, Pablo; Periquet, Magali; Laine, Sophie; Debarges, Beatrice; Lesage, Suzanne; Durr, Alexandra
CS Hop La Pitie Salpetriere, AP HP, Dept Gent Cytogenet and Embryol, INSERM,U679, 47 Blvd Hop, F-75651 Paris 13, France
brice@ccr.jussieu.fr
SO Cummings, J [Editor]; Hardy, J [Editor]; Poncet, M [Editor]; Christen, Y [Editor]. (2005) pp. 153-164. Research and Perspectives in Alzheimer's Disease.
Publisher: SPRINGER-VERLAG BERLIN, HEIDELBERGER PLATZ 3, D-14197 BERLIN,
GERMANY. Series: RESEARCH AND PERSPECTIVES IN ALZHEIMERS DISEASE.
ISSN: 0945-6066. ISBN: 3-540-24835-8(H).
DT Book; (Book Chapter)
LA English
ED Entered STN: 17 May 2006
Last Updated on STN: 17 May 2006

L2 ANSWER 6 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2005:452533 BIOSIS <<LOGINID::20070510>>
DN PREV200510239184
TI Neurodegenerative disorders: Parkinson's disease and Huntington's disease.
AU Hague, S. M.; Klaffke, S.; Bandmann, O. [Reprint Author]
CS Univ Sheffield, Sch Med, Acad Neurol Unit, Div Genom Med, E Floor,Beech Hill Rd, Sheffield S10 2RX, S Yorkshire, UK
o.bandmann@sheffield.ac.uk
SO Journal of Neurology Neurosurgery & Psychiatry, (AUG 2005) Vol. 76, No. 8, pp. 1058-1063.
CODEN: JNNPAU. ISSN: 0022-3050.
DT Article
LA English
ED Entered STN: 3 Nov 2005
Last Updated on STN: 3 Nov 2005
AB Parkinson's disease and Huntington's disease are both model diseases. Parkinson's disease is the most common of several akinetic-rigid syndromes and Huntington's disease is only one of an ever growing number of trinucleotide repeat disorders. Molecular genetic studies and subsequent molecular biological studies have provided fascinating new insights into

the pathogenesis of both disorders and there is now real hope for disease modifying treatment in the not too distant future for patients with Parkinson's disease or Huntington's disease.

L2 ANSWER 7 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
DUPLICATE 2
AN 2004:238680 BIOSIS <<LOGINID::20070510>>
DN PREV200400239095
TI PIASgamma represses the transcriptional activation induced by the nuclear receptor Nurr1.
AU Galleguillos, Danny; Vecchiola, Andrea; Fuentealba, Jose Antonio; Ojeda, Viviana; Alvarez, Karin; Gomez, Andrea; Andres, Maria Estela [Reprint Author]
CS Departamento de Biologia Celular y Molecular, Facultad de Ciencias Biologicas, Pontificia Universidad Catolica de Chile, Alameda 340, P. O. Box 114-D, Santiago, Chile
mandres@bio.puc.cl
SO Journal of Biological Chemistry, (January 16 2004) Vol. 279, No. 3, pp. 2005-2011. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DT Article
LA English
ED Entered STN: 6 May 2004
Last Updated on STN: 6 May 2004
AB Nurr1 is a transcription factor essential for the development of ventral dopaminergic neurons. In search for regulatory mechanisms of Nurr1 function, we identified the SUMO (small ubiquitin-like modifier)-E3 ubiquitin-protein isopeptide ligase, PIASgamma, as an interaction partner of Nurr1. Overexpressed PIASgamma and Nurr1 co-localize in the nuclei of transfected cells, and their interaction is demonstrated through co-immunoprecipitation and glutathione S-transferase pulldown assays. Co-expression of PIASgamma with Nurr1 results in a potent repression of Nurr1-dependent transcriptional activation of an artificial NGFI-B response element (NBRE) reporter as well as of a reporter driven by the native tyrosine hydroxylase promoter. We identified two consensus sumoylation sites in Nurr1. The substitution of lysine 91 by arginine in one SUMO site enhanced the transcriptional activity of ***Nurr1*** , whereas the ***substitution*** of lysine 577 by arginine in the second SUMO site decreased transcriptional activity of Nurr1. Interestingly, PIASgamma-induced repression of Nurr1 activity does not require the two sumoylation sites, because each mutant is repressed as efficiently as the wild type Nurr1. In addition, the ***mutations*** do not alter ***Nurr1*** nuclear localization. Finally, we provide evidence that Nurr1 and PIASgamma co-exist in several nuclei of the rodent central nervous system by demonstrating the co-expression of Nurr1 protein and PIASgamma mRNA in the same cells. In conclusion, our studies identified PIASgamma as a transcriptional co-regulator of Nurr1 and suggest that this interaction may have a physiological role in regulating the expression of Nurr1 target genes.

L2 ANSWER 8 OF 35 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 2005033530 EMBASE <<LOGINID::20070510>>
TI ***Nurr1*** ***mutational*** screen in Parkinson's disease.
AU Tan E.-K.; Chung H.; Chandran V.R.; Tan C.; Shen H.; Yew K.; Pavanni R.; Puvan K.-A.; Wong M.-C.; Teoh M.-L.; Yih Y.; Zhao Y.
CS Dr. E.-K. Tan, Department of Neurology, Singapore General Hospital, Outram Road, Singapore 169608, Singapore. gnrtek@sgh.com.sg
SO Movement Disorders, (2004) Vol. 19, No. 12, pp. 1503-1505. .
Refs: 20
ISSN: 0885-3185 CODEN: MOVDEA
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
022 Human Genetics
029 Clinical Biochemistry
LA English
SL English
ED Entered STN: 4 Feb 2005
Last Updated on STN: 4 Feb 2005
AB We performed sequence analysis of all the exons and exon-intron boundaries in familial and young-onset Parkinson's disease (PD) in an Asian cohort. None of the patients carried any pathogenic ***mutations*** in the ***Nurr1*** gene. We demonstrated a 5 to 10% prevalence of the intron 7 +33 C.fwdarw.T variant among Malay and Indian PD and healthy controls, suggesting that this variant, which was previously described only in 1 Chinese patient, was not a silent mutation but a common polymorphic variant in some ethnic races. .COPYRGT. 2004 Movement Disorder Society.

L2 ANSWER 9 OF 35 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 2004379345 EMBASE <<LOGINID::20070510>>
TI Evaluation of the role of Nurr1 in a large sample of familial Parkinson's disease.
AU Nichols W.C.; Uniacke S.K.; Pankratz N.; Reed T.; Simon D.K.; Halter C.; Rudolph A.; Shults C.W.; Conneally P.M.; Foroud T.; Wojcieszek J.; Belden J.; Carter J.; Camicioli R.; Andrews P.; Panisset M.; Hall J.; Hubble J.; Fernandez M.; Reider C.; Rajput A.; Rajput A.; Shirley T.; Mendis T.; Grimes D.A.; Gray P.; Ramos C.S.; Roque S.; Pfeiffer R.; Pfeiffer B.; Elmer L.; Davis K.; Friedman J.; Fernandez H.; Lannon M.; Reich S.; Dunlop B.; Seeberger L.; O'Brien C.; Judd D.; Hauser R.; Zesiewicz T.; Delgado H.; Shults C.; Fontaine D.; Jennings D.; Marek K.; Mendick S.; Aminoff M.; DiMinno M.; Lewitt P.; DeAngelis M.; Pahwa R.; Thomas S.; Truong D.; Pathak M.; Tran A.; Rodnitzky R.; Dobson J.; Koller W.; Weiner W.; Lyons K.; Kurlan R.; Berry D.; Bertoni J.; Peterson C.; Martin W.; Tuite P.; Schacherer R.; Marder K.; Harris J.; Jankovic J.; Hunter C.; Lang A.; Kleimer-Fisman G.; Nieves A.; So J.; Factor S.; Evans S.; Manyam B.; Wulbrecht B.; Walker F.; Hunt V.; Gordon M.F.; Hamman J.; Kang U.J.; Young J.; Blindauer K.; Petit J.; Rao J.; Cook M.; Stacy M.; Williamson K.; Pullman R.S.; Boyar K.; Leehey M.; Derian T.; Gordon P.; Werner J.; et al.
CS Dr. W.C. Nichols, Division of Human Genetics, Cincinnati Children's Hosp. Med. Ctr., 3333 Burnet Avenue, Cincinnati, OH 45229, United States.
bill.nichols@cchmc.org
SO Movement Disorders, (2004) Vol. 19, No. 6, pp. 649-655. .
Refs: 40
ISSN: 0885-3185 CODEN: MOVDEA
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
022 Human Genetics
029 Clinical Biochemistry
LA English
SL English
ED Entered STN: 24 Sep 2004
Last Updated on STN: 24 Sep 2004
AB Parkinson's disease (PD) is a common neurodegenerative disorder in humans with wide variability in the age of disease onset. Although the disease has been thought previously to occur sporadically in most patients, there is increasing evidence of a genetic contribution to the disorder. Recently, a polymorphic variant within intron 6 of the Nurr1 gene was reported to be associated with sporadic and familial PD. In an effort to identify susceptibility genes for PD, we have collected 783 PD patients from 372 families and 397 healthy controls from 217 families. PD patients and healthy controls were genotyped for the intron 6 insertion polymorphism by BseRI restriction endonuclease digestion. No significant difference in either homozygosity or heterozygosity for the 7048G7049 (IVS6 1361 +16insG) polymorphism was detected in the PD patient cohort as compared with the panel of healthy controls. Moreover, direct sequencing of exon 1 of the Nurr1 gene in PD patients failed to detect either of the two recently reported ***Nurr1*** ***mutations*** identified in a small subset of a PD patient cohort. Taken together, these data suggest that genetic alteration at the Nurr1 locus is not a significant risk factor for the development of Parkinson's disease in our large sample of familial PD patients. .COPYRGT. 2004 Movement Disorder Society.

L2 ANSWER 10 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2004:600987 CAPLUS <<LOGINID::20070510>>
DN 141:155222
TI Assessment of Nurr1 nucleotide variations in familial Parkinson's disease
AU Levecque, C.; Destee, A.; Mouroux, V.; Amouyel, P.; Chartier-Harlin, M.-C.
CS INSERM 508, Institut Pasteur de Lille, Lille, 59019, Fr.
SO Neuroscience Letters (2004), 366(2), 135-138
CODEN: NELED5; ISSN: 0304-3940
PB Elsevier Ltd.
DT Journal
LA English
AB Parkinson's disease (PD) is characterized by the death of dopaminergic neurons of the substantia nigra. As Nurr1 seems to regulate the development and maintenance of these neurons, we evaluated its potential role in Parkinson's disease using genetic methods. We genotyped two polymorphisms and screened a case-control sample for the presence/absence of two mutations recently described in exon 1. Our results failed to replicate the assocn. initially obsd. and none of the mutations were present in our familial Parkinson's disease cases. These observations suggest that this gene is unlikely to play a major effect in French familial Parkinson disease.
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2006:18 BIOSIS <<LOGINID::20070510>>
DN PREV200600009511
TI Dopaminergic properties and anti-Parkinsonian effects of IPX750 in rodent models of Parkinson's disease.
AU Jiang, Chuantao [Reprint Author]; Wan, Xinhua; Jankovic, Joseph; Christian, Samuel T.; Sundsmo, John S.; Le, Weidong
SO Neurology, (APR 13 2004) Vol. 62, No. 7, Suppl. 5, pp. A9.
Meeting Info.: 56th Annual Meeting of the American-Academy-of-Neurology. San Francisco, CA, USA. April 24 -May 01, 2004. Amer Acad Neurol.
CODEN: NEURAI. ISSN: 0028-3878.
DT Conference; (Meeting)
Conference; (Meeting Poster)
LA English
ED Entered STN: 14 Dec 2005
Last Updated on STN: 14 Dec 2005

L2 ANSWER 12 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2003:117961 CAPLUS <<LOGINID::20070510>>
DN 138:168235
TI Alleles of the NURR1 gene associated with lowered tyrosine hydroxylase

levels and familial Parkinson's disease
IN Le, Wei-Dong; Vassilatis, Demetrios K.
PA Baylor College of Medicine, USA
SO PCT Int. Appl., 201 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003012040	A2	20030213	WO 2002-US23766	20020712
WO 2003012040	A3	20030703		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003119026	A1	20030626	US 2002-205951	20020726
US 7037657	B2	20060502		
PRAI US 2001-308294P	P	20010727		

AB The identification of ***mutation*** in ***NURR1*** provides mol. tools for the development of diagnostic, prophylactic and therapeutic agents for Parkinson's Disease. In specific embodiments, two point mutations are identified in exon 1 of the NURR1 gene in 10/107 (9.3 %) cases of familial Parkinson's disease (PD). The ***mutations*** reduce ***NURR1*** gene expression (mRNA and protein levels) by 87-95 % and decrease tyrosine hydroxylase (a rate-limited dopamine synthesis enzyme) gene expression in vitro. It is also demonstrated that in vivo NURR1 mRNA levels in the lymphocytes from the PD patients with the exon 1 mutation are reduced by 68-84 %, and in over 50 % sporadic PD patients the NURR1 mRNA levels in lymphocytes are significantly reduced. A homozygous polymorphism is identified in intron 6 of NURR1 that correlates with the presence of Parkinson's disease. A splicing variant in NURR1 exon 5 is identified.

L2 ANSWER 13 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 3
AN 2003:438958 BIOSIS <<LOGINID::20070510>>
DN PREV200300438958
TI Decreased ethanol preference and wheel running in Nurr1-deficient mice.
AU Werme, Martin; Hermanson, Elisabet; Carmine, Andrea; Buervenich, Silvia; Zetterstrom, Rolf H.; Thoren, Peter; Ogren, Sven Ove; Olson, Lars; Perlmann, Thomas; Brene, Stefan [Reprint Author]
CS Department of Neuroscience, Karolinska Institutet, S-171 77, Stockholm, Sweden
stefan.brene@neuro.ki.se
SO European Journal of Neuroscience, (June 2003) Vol. 17, No. 11, pp. 2418-2424. print.
ISSN: 0953-816X (ISSN print).
DT Article
LA English
ED Entered STN: 24 Sep 2003
Last Updated on STN: 24 Sep 2003
AB Nurr1 (Nr4a2) is a transcription factor expressed in dopamine cells from early development and throughout life. Null mutants for Nurr1 lack the ventral midbrain dopamine neurons and die soon after birth. Animals with a heterozygous deletion are viable and display no apparent abnormality. We have investigated the impact of heterozygous ***deletion*** of ***Nurr1*** on ethanol consumption in adult mice as a model for drug-induced reward and on wheel running as a model for natural reward. Interestingly, Nurr1 heterozygous mice never developed high ethanol consumption nor did they develop as much running behaviour as did the wild-type animals. Thus, Nurr1 appears to have a key role for the reinforcing properties of ethanol and running that underlies the development of excessive reward-seeking behaviours characteristic for addiction. Quantitative trait loci mapping using C57Bl/6 and DBA/2 mice describe a locus for ethanol preference on chromosome 2, wherein Nurr1 is located. We found two dinucleotide repeats in the Nurr1 promoter that were longer in mice with low preference for ethanol (DBA/2 and 129/Sv) than in mice with high preference for ethanol (C57Bl/6J and C57Bl/6NIH). These sequential data are compatible with Nurr1 as a candidate gene responsible for the quantitative trait loci for ethanol preference on mouse chromosome 2. Together, our data thus imply involvement of Nurr1 in the transition to a state of high ethanol consumption as well as in the development of a high amount of wheel running in mice.

L2 ANSWER 14 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN
AN 2004:133680 BIOSIS <<LOGINID::20070510>>
DN PREV200400132100
TI In vitro studies to assess predictive biomarkers of interferon induced depression.
AU Cai, Wei [Reprint Author]; Khaoustov, Vladimir I. [Reprint Author]; Xie, Qing [Reprint Author]; Pan, Tianhong [Reprint Author]; Le, Weidong [Reprint Author]; Yoffe, Boris [Reprint Author]
CS Baylor College of Medicine, Houston, TX, USA
SO Hepatology, (October 2003) Vol. 38, No. 4 Suppl. 1, pp. 634A. print.
Meeting Info.: 54th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA, USA. October 24-28, 2003. American Association for the Study of Liver Diseases.
ISSN: 0270-9139 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 10 Mar 2004
Last Updated on STN: 10 Mar 2004
AB Background & Aims: Depression is a relative contraindication for the treatment of hepatitis C with alpha interferon (IFN). Up to 40% of patients develop clinically significant depression during IFN therapy. The pathophysiology of INF-induced depression remains poorly understood. Glucocorticoid (GR) and serotonin (SR) receptors are primarily involved in termination of the stress response. Also, it was observed that ***mutations*** in ***Nurr1*** gene, a member of nuclear receptor superfamily, are associated with depression related to dopaminergic dysfunction. Recently, we reported that IFN downregulats GR expression in vitro in lymphoid and hepatocyte derived cell lines (Hepatology 2002;36(4): 284A). To expand these observations and to gain better insight of IFN-induced depression we initiated studies to assess additional cell lines including neuroblastoma and to evaluate effects of IFN on serotonin and dopamine pathways. Microarray technology was used to identify novel depression-related genes. Methods and Results: To assess the role of GR, SR, and Nurr1 in IFN induced depression, a variety of cell lines were treated with different concentrations of IFN (1 to 300 ng/ml), respectively. We used Western blot, RT-PCR and the Affymetrix GeneChip Arrays. Hepatoblastoma (Huh7), T cell leukemia-derived (Jurkat), neuroblastoma (SH5YSY), and myelocyte-derived (P815) cell lines were assessed for IFN effects. Although, the dose- and incubation time-dependent decreases of GR, SR, and Nurr1 levels were observed, the effect of IFN was more profound in lymphoid- and myelocyte-derived cell lines (GR decreased at least by 70%). To assess the recovery time of GR and SR following maximized IFN-induced downregulation, Jurkat cells were treated with IFN for 72 hours and than for additional 24, 48 and 72 hours with or without IFN. Expression of SR paralleled results obtained with GR and demonstrated at least partial recovery at 72 hr. Also, coincubation with tricyclic antidepressant (desipramine) or serotonin reuptake inhibitors (fluoxetine) decreased by at least 50% the effect of IFN on GR and SR. Assessment of dopamine pathway following IFN treatment in neuroblastoma cells revealed a significant suppression of the expression of Nurr1 (up to 68%) which was determined by quantitative real-time PCR. Interestingly, in contrast to GR or SR, the suppression of Nurr1 mRNA by IFN lasted longer. To confirm our results and to search for novel genes involved in the development of depressive disorders, we performed initial analyses by Affymetrix GeneChip Array. The Array confirmed downregulation of several serotonin and glucocorticoids related genes. In contrast, expressions of at least 400 genes (not related to serotonin and dopamine) were increased from 2 to 100 folds after IFN treatment. Conclusions: In summary, we demonstrated that in vitro a) IFN downregulates GR and SR levels in both hematopeitic and liver derived cell lines and that these effects are reversed within 72 hrs; b) addition of desipramine or SSRI abolishes the effect IFN, c) treatment with IFN in neuroblastoma cell line significantly suppressed the expression of Nurr1 suggesting involvement of dopamine pathway. These data provide insight regarding pathogenesis of IFN-induced psychiatric disorders. If these in vitro results can be corroborated in the clinical setting, they may provide a powerful tool for predicting the development of depression and may afford an opportunity to tailor specific therapy for individuals undergoing treatment for hepatitis C.

L2 ANSWER 15 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 4
AN 2003:442877 BIOSIS <<LOGINID::20070510>>
DN PREV200300442877
TI Elevated locomotor activity without altered striatal dopamine contents in Nurr1 heterozygous mice after acute exposure to methamphetamine.
AU Backman, Cristina [Reprint Author]; You, Zhi-Bing; Perlmann, Thomas; Hoffer, Barry J.
CS Cellular Neurobiology Branch, National Institute on Drug Abuse, 5500 Nathan Shock Drive, Baltimore, MD, 21221, USA
cbackman@intra.nida.nih.gov
SO Behavioural Brain Research, (14 July 2003) Vol. 143, No. 1, pp. 95-100. print.
CODEN: BBREDI. ISSN: 0166-4328.
DT Article
LA English
ED Entered STN: 24 Sep 2003
Last Updated on STN: 24 Sep 2003
AB Gene targeting experiments, in which both alleles of the ***Nurr1*** gene were ***deleted*** , have shown that this molecule plays an essential role in the development of midbrain dopaminergic neurons, as shown by the loss of dopaminergic markers and the neurotransmitter dopamine (DA) in the ventral mesencephalon of Nurr1 null mutant mice. Nurr1-deficient mice die within a few hours of birth. Herein, we investigated whether adult mice (12-15-month-old), heterozygous for the ***Nurr1*** ***mutation*** (***Nurr1*** +/-), show alterations in locomotor function and in the nigrostriatal dopaminergic system after acute exposure to methamphetamine. We first evaluated spontaneous and amphetamine-induced (5 mg/kg) locomotor response of >12-month-old wildtype (Nurr1+/+) and Nurr1+/- mice. Both, spontaneous and methamphetamine-

induced locomotor behavior was significantly increased in the Nurr1+/- animals as compared to Nurr1+/+ mice. Striatal DA and DA metabolite levels were measured in untreated animals and methamphetamine-treated animals. No significant differences in striatal dopamine levels or its metabolites DOPAC and HVA were found in the Nurr1+/- as compared to Nurr1+/+ mice in untreated or methamphetamine-treated animals. These data show that deletion of a single allele of the Nurr1 gene alters the locomotor activity of 12-15-month-old Nurr1+/- animals. While total dopamine levels were not altered in the striatum of Nurr1+/- mice, future studies will be necessary to determine if processes involved with the dynamics of DA release/clearance within the nigrostriatal system may be altered in Nurr1+/- mutant mice.

L2 ANSWER 16 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2004:205866 BIOSIS <<LOGINID::20070510>>
DN PREV200400206382
TI Rota - rod and locomotor activity performance in Nurr1 knock - out mice.
AU Jiang, C. [Reprint Author]; Le, W. [Reprint Author]
CS Neurol., Baylor Col. of Med., Houston, TX, USA
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 916.18. http://sfn.scholarone.com. e-file. Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004
AB Objectives: ***Mutation*** in ***Nurr1*** gene, encoding a transcription factor, causes selective agenesis of dopaminergic neurons in the midbrain. To study the role of Nurr1 gene expression in modulating the function of dopaminergic neurons, we performed several animal behavioral tests to determine whether Nurr1 deficiency in mice can manifest abnormal behaviors associated with Parkinsonis disease (PD).Methods: In the present study we compared the changes of rotarod performance and locomotor activities in Nurr1+/-mice with MPTP-lesioned (i.p. 15mg/kg, every 2 hours x 4 times) mice. The rotarod performance was conducted on the Economex Rota-rod and the locomotor activity measurement was conducted on automatic locomotive analysers. We tested a series of behavioral performances for each animal at different time points and every behavioral test was performed for 3 times and the average values were calculated for the statistic analysis.Results: We found that (1) the Nurr1+/-male mice had significantly decreased rotarod performance by 43% as compared with wild-type (WT) male mice, while the females showed no significant difference. (2) The rotarod time significantly decreased in aged Nurr1+/-male mice as compared with WT male mice. (3) The stress-driven locomotor activities were significantly increased in both Nurr1+/-male mice and MPTP-lesioned male mice.Conclusion: We conclude that
(1) only male Nurr1+/-mice showed significantly decreased rotarod performance as compared with WT male mice. (2) The behavioral changes associated with the dysfunction of central dopaminergic neurons in Nurr1+/-male mice were similar to that seen in MPTP-lesioned male mice, but they were subjected to deterioration with aging, suggesting that the Nurr1+/-mouse is a very useful animal model to study PD.

L2 ANSWER 17 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2004:205523 BIOSIS <<LOGINID::20070510>>
DN PREV200400206039
TI Expression of differentially active isoforms of Nurr1 in ventral midbrain.
AU Michelhaugh, S. K. [Reprint Author]; Wang, J. [Reprint Author]; Mendiratta, V. [Reprint Author]; Bannon, M. J. [Reprint Author]
CS Dept. of Psychiatry and Behavioral Neurosci., Wayne State Univ., Detroit, MI, USA
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 897.12. http://sfn.scholarone.com. e-file. Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 14 Apr 2004
Last Updated on STN: 14 Apr 2004
AB Nurr1 is a transcription factor required for the acquisition and maintenance of the dopaminergic phenotype of the neurons of the substantia nigra. In nurr1 knockout mice, neurons of the substantia nigra do not develop a dopamine phenotype. Conversely, overexpression of nurr1 in embryonic stem cells is sufficient to produce a dopaminergic phenotype. This may be due to the ability of nurr1 to regulate expression of the tyrosine hydroxylase and dopamine transporter genes. Recent studies have also shown that nurr1 expression is decreased in cocaine overdose victims and decreases during the course of normal human aging. ***Mutations*** of ***nurr1*** have also been implicated to play a role in familial Parkinson's disease. Alternative splice sites in the ***nurr1*** gene produce internal ***deletions*** or truncated forms missing the amino-or carboxy-terminus. As both termini contain activation function domains, loss of either or both could dramatically affect nurr1 activity. Here we identify expression of multiple splice variants in rat ventral mesencephalon by RT-PCR and examine the functional activity of these splice variants in dopaminergic SN4741 cells. Activity of all examined nurr1 variants was decreased in comparison to full length nurr1.

L2 ANSWER 18 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2004:145901 BIOSIS <<LOGINID::20070510>>
DN PREV200400145720
TI Characterization of ribozymes against Nurr1 to study its role in the adult brain.
AU Burger, C. [Reprint Author]; Fuentealba, J.; Nash, K. [Reprint Author]; Muzyczka, N. [Reprint Author]; Andres, M.
CS Dept. Mol. Genet. and Microbiol, Univ. Florida, Catholic Univ. of Chile, Santiago, Chile
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 778.11. http://sfn.scholarone.com. e-file. Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004
AB Nurr1 is a transcription factor that belongs to the nuclear receptor superfamily. It has been demonstrated that Nurr1 is essential for the development of ventral dopaminergic neurons. However, the role of Nurr1 in adult animals is unknown. Recently, two different ***mutations*** in the ***Nurr1*** gene have been mapped in familial cases of Parkinson's disease. In order to analyze the role of Nurr1 in the adult brain, we propose to use a novel approach to create Nurr1 somatic knockouts by using ribozymes (enzymes that cleave RNA in a sequence-specific manner) and the adeno-associated virus (rAAV) viral gene delivery system. We have generated three ribozymes that cleave the Nurr1 mRNA in a sequence specific manner: Nurr1363, Nurr1844 and Nurr1869. The kinetic properties of these ribozymes were analyzed and the results shown in the table. Vectors containing these ribozymes will be packaged into AAV5 capsids, and the virus will be injected into selected nuclei of the rat brain. This in vivo study in adult animals will allow us to understand how Nurr1 regulates the mature dopaminergic phenotype.

L2 ANSWER 19 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2002:575228 CAPLUS <<LOGINID::20070510>>
DN 137:136161
TI Nurr1 transcription factor I-box mutants having monomeric transcriptional activation activity but unable to dimerize with retinoid X receptor
IN Perlmann, Thomas; Aarnisalo, Piia
PA Ludwig Institute for Cancer Research, USA
SO PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002059303	A1	20020801	WO 2002-EP744	20020125
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002249140	A1	20020806	AU 2002-249140	20020125
EP 1354044	A1	20031022	EP 2002-718046	20020125
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004519227	T	20040702	JP 2002-559789	20020125
US 2004076995	A1	20040422	US 2003-470156	20030724
PRAI GB 2001-2087	A	20010126		
WO 2002-EP744	W	20020125		

AB The invention relates to the finding that the Nurr1 transcription factor, which forms a heterodimer with the retinoid X receptor, can be mutated in the I box region such that dimerization does not occur while Nurr1 transcriptional activation activity is retained. The invention provides Nurr1 peptides with such I box mutations, as well as assay methods for modulators which affect the monomeric activity of Nurr1. The three amino acid alanine substitutions were introduced to the I-box [KLL(554-556)AAA, GKL(557-559)AAA, and PEL(560-562)AAA] and all these mutations abolished the ability of Nurr1 to promote RXR-mediated transactivation, but the ability to activate reporter gene expression as monomers was, however, intact. Mutation of the Pro560 to alanine abolished the ability of Nurr1 to activate reporter gene expression as a dimer with RXR but had no effect on monomeric activity. Conversion of Lys558 to alanine had only a modest effect on Nurr1/RXR heterodimer-mediated transactivation. The ability of Nurr1 to activate the Nurr1-RXR heterodimer-regulated reporter gene was reduced by the substitution of Leu562 by alanine but to a lesser extent than by the P560A mutation. N-terminal truncations of the full length protein also retained transcription activation activity.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 20 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 5
AN 2002:583821 BIOSIS <<LOGINID::20070510>>
DN PREV200200583821
TI Defining requirements for heterodimerization between the retinoid X receptor and the orphan nuclear receptor Nurr1.
AU Aarnisalo, Piia; Kim, Chae-Hee; Lee, Jae Woon; Perlmann, Thomas [Reprint author]
CS Ludwig Institute for Cancer Research, Karolinska Institute, Stockholm, SE 171 77, Sweden
thomas.perlmann@licr.ki.se
SO Journal of Biological Chemistry, (September 20, 2002) Vol. 277, No. 38, pp. 35118-35123. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DT Article
LA English
ED Entered STN: 13 Nov 2002
Last Updated on STN: 13 Nov 2002
AB Nurr1, an orphan nuclear receptor mainly expressed in the central nervous system, is essential for the development of the midbrain dopaminergic neurons. Nurr1 binds DNA as a monomer and exhibits constitutive transcriptional activity. Nurr1 can also regulate transcription as a heterodimer with the retinoid X receptor (RXR) and activate transcription in response to RXR ligands. However, the specific physiological roles of Nurr1 monomers and RXR-Nurr1 heterodimers remain to be elucidated. The aim of this study was to define structural requirements for RXR-Nurr1 heterodimerization. Several amino acid substitutions were introduced in both Nurr1 and RXR in the I-box, a region previously shown to be important for nuclear receptor dimerization. Single amino acid ***substitutions*** introduced in either ***Nurr1*** or RXR abolished heterodimerization. Importantly, heterodimerization-deficient Nurr1 mutants exhibited normal activities as monomers. Thus, by introducing specific amino acid ***substitutions*** in ***Nurr1*** , monomeric and heterodimeric properties of Nurr1 can be distinguished. Interestingly, substitutions in the RXR I-box differentially affected heterodimerization with Nurr1, retinoic acid receptor, thyroid hormone receptor, and constitutive androstane receptor demonstrating that the dimerization interfaces in these different heterodimers are functionally unique. Furthermore, heterodimerization between RXR and Nurr1 had a profound influence on the constitutive activity of Nurr1, which was diminished as a result of RXR interaction. In conclusion, our data show unique structural and functional properties of RXR-Nurr1 heterodimers and also demonstrate that specific ***mutations*** in ***Nurr1*** can abolish heterodimerization without affecting other essential functions.

L2 ANSWER 21 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 6
AN 2002:256311 BIOSIS <<LOGINID::20070510>>
DN PREV200200256311
TI Association of homozygous 7048G7049 variant in the intron six of Nurr1 gene with Parkinson's disease.
AU Xu, P.-Y.; Liang, R.; Jankovic, J.; Hunter, C.; Zeng, Y.-X.; Ashizawa, T.; Lai, D.; Le, W.-D. [Reprint author]
CS Department of Neurology, Baylor College of Medicine, 6501 Fannin Street, Houston, TX, 77030, USA
Weidongl@bcm.tmc.edu
SO Neurology, (March 26, 2002) Vol. 58, No. 6, pp. 881-884. print.
CODEN: NEURAI. ISSN: 0028-3878.
DT Article
LA English
ED Entered STN: 24 Apr 2002
Last Updated on STN: 24 Apr 2002
AB Objective: To determine whether the Nurr1 gene, which is critical for the development and maintenance of nigral dopaminergic neurons, is a risk factor associated with PD. Background: The Nurr1 gene is highly expressed in the dopaminergic neurons in the midbrain. Knockout of the gene results in agenesis of nigral dopaminergic neurons and heterozygous knockout mice increases 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity. Methods: This study included 105 patients with familial PD (fPD) and 120 patients with sporadic PD (sPD) and 221 age-matched healthy control subjects. The polymorphisms and ***mutations*** of the ***Nurr1*** gene in patients with PD were initially examined by heteroduplex analysis and sequencing analysis from PCR-amplified Nurr1 gene fragments. A polymorphism in the BseRI restriction site was identified, and a relatively large-scale analysis then was conducted by three independent investigators who were blinded to the clinical status of the subjects. Results: A homozygous 7048G7049 polymorphism was found in intron 6 of the Nurr1 gene, which was significantly higher in fPD (10/105; 9.5%) and in sPD (5/120; 4.2%) compared with healthy control subjects (2/221; 0.9%). The mean age and the SD at onset of these homozygote patients with PD was 52+-15 years for fPD and 46+-7 years for sPD. The clinical features of these homozygote patients with PD did not differ from those of typical PD. Conclusions: The homozygote polymorphism of 7048G7049 in intron 6 of the Nurr1 gene is associated with typical PD.

L2 ANSWER 22 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN
AN 2002:554057 BIOSIS <<LOGINID::20070510>>
DN PREV200200554057
TI ***Nurr1*** gene ***mutations*** in PD.
AU Le, Wei-dong [Reprint author]; Xu, Pingyi [Reprint author]; Jiang, Hong [Reprint author]; Appel, Stanley H. [Reprint author]; Smith, Roy G. [Reprint author]; Vassilatis, Demetrios K.; Jankovic, Joseph [Reprint author]
CS Houston, TX, USA
SO Neurology, (April 9, 2002) Vol. 58, No. 7 Supplement 3, pp. A409. print.
Meeting Info.: 54th Annual Meeting of the American Academy of Neurology. Denver, Colorado, USA. April 13-20, 2002.
CODEN: NEURAI. ISSN: 0028-3878.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 30 Oct 2002
Last Updated on STN: 30 Oct 2002

L2 ANSWER 23 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 7
AN 2002:428035 BIOSIS <<LOGINID::20070510>>
DN PREV200200428035
TI Dopamine neurons heterozygous for the Nurr1-null allele have reduced survival in vitro.
AU Eells, J. B.; Yeung, S. K.; Nikodem, V. M. [Reprint author]
CS National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, 20892, USA
SO Neuroscience Research Communications, (May-June, 2002) Vol. 30, No. 3, pp.
173-183. print.
CODEN: NRCOEE. ISSN: 0893-6609.
DT Article
LA English
ED Entered STN: 7 Aug 2002
Last Updated on STN: 7 Aug 2002
AB Although Nurr1 is essential for the differentiation of midbrain dopamine neurons, its function in mature dopamine neurons has not been determined. In order to investigate the role of Nurr1 in the survival of dopamine neurons, neurons from the mesencephalon of newborn pups heterozygous for the ***Nurr1*** -null ***mutation*** (+/-) or wild-type (+/+) littermates were grown in culture. Postnatal cultures revealed a significant reduction in the survival and growth of tyrosine hydroxylase immunoreactive (TH-IR) neurons from Nurr1 +/- pups as early as 1 day in culture despite having normal TH-IR neuron numbers in vivo. The Nurr1 +/+ and +/- TH-IR neurons responded to treatment with forskolin, glia cell-line derived neurotrophic factor and brain-derived neurotrophic factor, although significantly fewer Nurr1 +/- TH-IR neurons survived. These data suggest that the loss of a single allele of Nurr1 significantly reduces the survival capacity of postnatal dopamine neurons in vitro without affecting normal development or differentiation.

L2 ANSWER 24 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN
AN 2003:325903 BIOSIS <<LOGINID::20070510>>
DN PREV200300325903
TI ASSOCIATION OF POLYMORPHISMS WITHIN THE NURR1 (NR4A2) PROMOTER AND
UNTRANSLATED REGIONS WITH SCHIZOPHRENIA AND PERSONALITY TRAITS.
AU Carmine, A. [Reprint Author]; Buervenich, S. [Reprint Author]; Galter, D. [Reprint Author]; Jonsson, E. G.; Sedvall, G. C.; Farde, L.; Gustavsson, J. P.; Bergman, H.; Anvret, M.; Nimgaonkar, V. L.; Chowdari, K. V.; Sydow, O.; Olson, L. [Reprint Author]
CS Neuroscience, Molecular Medicine, Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2002) Vol. 2002, pp. Abstract No. 706.17. http://sfn.scholarone.com. cd-rom.
Meeting Info.: 32nd Annual Meeting of the Society for Neuroscience. Orlando, Florida, USA. November 02-07, 2002. Society for Neuroscience.
DT Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 16 Jul 2003
Last Updated on STN: 16 Jul 2003
AB Missense ***mutations*** in the ***NURR1*** gene (now also termed NR4A2) in two patients with schizophrenia (SZ) and one patient with bipolar disease with psychotic symptoms have been described previously, white polymorphisms were found to be suspiciously absent from the coding region. The present study was aimed at examining the promoter region of NURR1 for polymorphic sites. Five variations were identified. Three of these polymorphisms were found to be in strong linkage disequilibrium with each other and a previously identified polymorphic site in the sixth intron (BseRI). One polymorphism of this common haplotype and two other independent polymorphisms were investigated for association with SZ and putative associated endophenoypes or personality traits by comparing their frequencies in 134 subjects with SZ and 204 matched controls. No significant genotype or allelic association with SZ was found. Only one sequence change showed a trend towards increased frequency in SZ patients (p=0.15 for genotypes and p=0.06 for allele frequencies). Several comparisons regarding endophenotypes or personality gave positive results at the 5% confidence level. Correction for multiple testing (Bonferroni) rendered none of these findings significant. The identified polymorphic

sites are thus unlikely to be major risk factors for SZ susceptibility in our sample.

L2 ANSWER 25 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 2001:12603 CAPLUS <<LOGINID::20070510>>
DN 134:81721
TI ***Mutations*** in the ***Nurr1*** gene associated with psychotic disorders and the development of disease models
IN Buervenich, Silvia; Olson, Lars; Anvret, Maria; Carmine, Andrea
PA Karolinska Innovations Ab, Swed.
SO PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001000807	A1	20010104	WO 2000-SE1380	20000629
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1194537	A1	20020410	EP 2000-946672	20000629
EP 1194537	B1	20061025		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY				
AT 343632	T	20061115	AT 2000-946672	20000629
PRAI SE 1999-2489	A	19990630		
WO 2000-SE1380	W	20000629		

AB The present invention relates to an isolated Nurr1 gene including one or more mutations selected from the group consisting of Met97Val (M97V), His103Arg (H103R), Tyr121del (Y121del) and Tyr122del (Y122del), or a functional fragment or variant thereof, as well as to proteins or peptides encoded thereof. The ***mutation*** in ***Nurr1*** gene significantly reduces the transcriptional activity of Nurr1 homodimers (30-40%)in in-vitro expression expt. Further, the invention also relates to cell cultures and transgenic animals comprising a mutated gene or a gene fragment as models for the study of psychotic disorders, such as schizophrenia and/or manic depressive disorder, as well as for the identification of effective therapies and drugs for the treatment of said disorders. In an addnl. aspect the invention relates to novel drugs developed by use of one or more of the mutations according to the invention for the treatment and/or prevention of psychotic disorders. Finally, the invention relates to methods of diagnostics wherein the mutations according to the invention are identified as well as to kits for performing such methods.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 26 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN
AN 2002:38785 BIOSIS <<LOGINID::20070510>>
DN PREV200200038785
TI Hitting dopamine neurons twice: Behavior of Nurr1-GDNF, Nurr1-GFRalpha1 and GDNF-GFRalpha1 double heterozygote knockouts.
AU Mattsson, A. [Reprint author]; Perlmann, T.; Zetterstrom, R. [Reprint author]; Tomac, A.; Westphal, H.; Hoffer, B.; Ogren, S. O. [Reprint author]; Olson, L. [Reprint author]
CS Dept. of Neuroscience, Karolinska Institutet, Stockholm, Sweden
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2628. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 2 Jan 2002
Last Updated on STN: 25 Feb 2002
AB Dopaminergic neurotransmission is etiologically and/or therapeutically implicated in Parkinson's disease, schizophrenia, bipolar disease, addiction and ADHD. To begin modeling diseases with multi-genetic background we have focused on three genes of importance for dopamine (DA) neurons: NURR1, a transcription factor strongly expressed in substantia nigra and VTA and crucial for development of midbrain dopaminergic neurons; GDNF, a potent dopaminotrophic factor assumed to promote postnatal survival of midbrain DA neurons; and GFRalpha-1, a GDNF-specific receptor component expressed by DA neurons. Homozygous deletion of any of these three genes is lethal, while heterozygotes survive to adulthood. We generated the three possible double heterozygous animals involving these genes and compared them with single heterozygous animals with regard to spontaneous and psychostimulant-induced locomotor activity. The compound heterozygous mice all exhibit a different locomotor behavior than the corresponding single heterozygotes. Thus mice with a heterozygous ***deletion*** of the ***Nurr1*** , GDNF or GFRalpha1 gene showed increased spontaneous and psychostimulant-induced locomotor activity in the order: Nurr1+/->GDNF+/- and GFRalpha1+/-. Double heterozygous mice instead tended to be hypoactive. Although genetic background is an important confounding factor, these results suggest that double heterozygous phenotypes cannot be deduced from knowledge about the corresponding single phenotypes.

L2 ANSWER 27 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN
AN 2002:22973 BIOSIS <<LOGINID::20070510>>
DN PREV200200022973
TI Effects of lithium treatment on hzf-3 and protein kinase C in different brain regions.
AU Ren, K. [Reprint author]; Agosto, J. L. [Reprint author]; Al-Banchaabouchi, M. [Reprint author]; Noel, M. [Reprint author]; Maldonado, J. [Reprint author]; Morales, E. [Reprint author]; Pena de Ortiz, S. [Reprint author]; Maldonado-Vlaar, C. S. [Reprint author]
CS Biol Dept, Univ Puerto Rico, San Juan, Puerto Rico
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2594. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 26 Dec 2001
Last Updated on STN: 25 Feb 2002
AB Lithium (Li) has been found to regulate neuronal signal transduction, synaptic plasticity, and gene transcription. However its molecular mechanism of action remains to be elucidated. Protein kinase C (PKC) is thought to mediate lithium effects. Hzf-3, a transcription factor known as ***Nurr1*** in mice, is ***mutated*** in schizophrenia and manic-depression cases and also play a role in learning. In order to investigate the effect of Li on PKC and hzf-3, two studies (Exp.) were conducted in several brain regions. Different time points were studied with two doses of LiCO3 (0.1% and 0.2%) in Long Evans rats. In Exp.1 using immunohistochemistry, hzf-3 levels were measured. Results showed that Li (0.2%) treatment at week 3, decreased hzf-3 protein levels in the hippocampus and substantia nigra but were increased in prefrontal cortex, nucleus accumbens and amygdala. In Exp.2 protein levels of several PKC isoforms were determined by western blots and immunohistochemistry and PKC activity assays were performed. Preliminary data showed that Li (0.1%) treatment at week 7, resulted in a decrease in PKC activity and its concentrations in the hippocampus and prefrontal cortex; an increase in the hypothalamus but no significant changes in the amygdala and nucleus accumbens. These data showed that hzf-3 and PKC are differentially affected in several brain areas by chronic Li treatment in the rat. Future studies will aim at investigating the region specificity and Li time course of action on these molecular effectors.

L2 ANSWER 28 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN
AN 2001:525962 BIOSIS <<LOGINID::20070510>>
DN PREV200100525962
TI Nurr1 is critical in both natural and drug-induced reward.
AU Brene, S. [Reprint author]; Werme, M. [Reprint author]; Hermansson, E.; Johansson, O. [Reprint author]; Zetterstrom, R. [Reprint author]; Perlmann, T.
CS Neuroscience, Karolinska Institutet, Stockholm, Sweden
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 1185. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 14 Nov 2001
Last Updated on STN: 23 Feb 2002
AB Mice lacking the Nurr1 gene do not have dopamine cells and die soon after birth. However, animals with a heterozygous deletion are viable and display no apparent abnormality. In the present study we have investigated the impact of a heterozygous ***deletion*** of the ***Nurr1*** gene in adult mice on ethanol intake and preference and wheel running activity. Nurr1 heterozygous mice were backcrossed to the C57 B1/6 strain for seven generations to minimize the genetic impact of the 129 strain in which the deletion was originally made. As a model for ethanol consumption, the two-bottle free-choice model was used in which the mice had free access to one bottle of water and one bottle of 10% ethanol. The Nurr1 +/+ mice developed a strong ethanol preference and consumed on average 9g ethanol/kg/day whereas the Nurr1 +/- mice consumed only 2g ethanol/day. The heterozygous animals had normal preference for saccharin and quinine solutions suggesting that Nurr1 does not effect taste sensations. Neither was ethanol metabolism changed by the ***deletion*** of the ***Nurr1*** gene. To test if Nurr1 not only has an impact on drug induced reward but also in natural reward mechanisms we analyzed the phenotype of Nurr1 heterozygous mice in running-wheels as a model for natural reward. When Nurr1 +/+ and Nurr1 +/- mice were placed in the running wheels the +/+ animals developed an excessive running behavior whereas the +/- did not. The results from the present study suggest that Nurr1 has a role in mechanisms controlling both natural and

drug induced reward in adult mice.

L2 ANSWER 29 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 8
AN 2001:64538 BIOSIS <<LOGINID::20070510>>
DN PREV200100064538
TI ***NURR1*** ***mutations*** in cases of schizophrenia and manic-depressive disorder.
AU Buervenich, Silvia; Carmine, Andrea; Arvidsson, Mariette; Xiang, Fengqing; Zhang, Zhiping; Sydow, Olof; Jonsson, Erik G.; Sedvall, Goran C.; Leonard, Sherry; Ross, Randal G.; Freedman, Robert; Chowdari, Kodavali V.; Nimgaonkar, Vishwajit L.; Perlmann, Thomas; Anvret, Maria; Olson, Lars [Reprint author]
CS Department of Neuroscience, Karolinska Institutet, 17177, Stockholm, Sweden
Lars.Olson@neuro.ki.se
SO American Journal of Medical Genetics, (December 4, 2000) Vol. 96, No. 6, pp. 808-813. print.
ISSN: 0148-7299.
DT Article
LA English
ED Entered STN: 31 Jan 2001
Last Updated on STN: 12 Feb 2002
AB Transgenic mice lacking the nuclear orphan transcription factor Nur-related receptor 1 (Nurr1) fail to develop mesencephalic dopamine neurons. There is a highly homologous NURR1 gene in humans (formerly known as NOT) which therefore constitutes a good candidate gene for neurologic and psychiatric disorders with an involvement of the dopamine neuron system, such as Parkinson's disease, schizophrenia, and manic-depression. By direct sequencing of genomic DNA, we found two different missense mutations in the third exon of NURR1 in two schizophrenic patients and another missense mutation in the same exon in an individual with manic-depressive disorder. All three mutations caused a similar reduction of in vitro transcriptional activity of NURR1 dimers of about 30-40%. Neither of these amino acid changes, nor any sequence changes whatsoever, were found in patients with Parkinson's disease or control DNA material of normal populations.

L2 ANSWER 30 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
AN 2001:97717 BIOSIS <<LOGINID::20070510>>
DN PREV200100097717
TI ***NURR1*** ***mutations*** in cases of schizophrenia and manic depressive disorder.
AU Carmine, A. [Reprint author]; Buervenich, S.; Arvidsson, M.; Xiang, F.; Zhang, Z.; Sydow, O.; Jonsson, E. G.; Sedvall, G. C.; Leonard, S.; Ross, R. G.; Freedman, R.; Chowdari, K. V.; Nimgaonkar, V. L.; Perlmann, T.; Anvret, M.; Olson, L.
CS Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden
SO Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-476.11. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 21 Feb 2001
Last Updated on STN: 15 Feb 2002
AB The development of mesencephalic dopamine neurons critically relies on the presence of functional Nur-related receptor 1 (Nurr1) protein, and mice lacking Nurr1 fail to develop this clinically important group of neurons. The highly homologous NURR1 (Formerly known as NOT) gene in humans therefore constitutes a good candidate gene for neurologic and psychiatric disorders with involvement of the dopamine neuron system, e.g. Parkinson's disease, schizophrenia and manic depression. By automated sequencing of genomic DNA from patients and controls, we found two different missense mutations in exon 3 of NURR1 in two schizophrenic patients and another missense mutation in the same exon in an individual with manic depressive disorder. In an in-vitro assay all three mutations caused a similar reduction of transcriptional activity of NURR1 dimers of about 30 to 40 percent. Neither of these three amino acid changes, nor any sequence change in coding regions whatsoever, were found in patients with Parkinson's disease or control DNA material of normal populations.

L2 ANSWER 31 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 9
AN 2000:1061 BIOSIS <<LOGINID::20070510>>
DN PREV200000001061
TI Reduced Nurr1 expression increases the vulnerability of mesencephalic dopamine neurons to MPTP-induced injury.
AU Le, Wei-dong [Reprint author]; Conneely, Orla M.; He, Y.; Jankovic, Joseph; Appel, Stanley H.
CS Department of Neurology, Baylor College of Medicine, 6501 Fannin Street, NB 302, Houston, TX, 77030, USA
SO Journal of Neurochemistry, (Nov., 1999) Vol. 73, No. 5, pp. 2218-2221. print.
CODEN: JONRA9. ISSN: 0022-3042.
DT Article
LA English
ED Entered STN: 23 Dec 1999
Last Updated on STN: 31 Dec 2001
AB ***Mutation*** in the ***Nurr1*** gene, a member of the nuclear receptor superfamily, causes selective agenesis of dopaminergic neurons in the midbrain of null mice. Homozygous Nurr1 knockout mice (Nurr1-/-) die 1 day after birth, but heterozygous mice (Nurr1+/-) survive postnatally without obvious locomotor deficits. Although adult Nurr1+/- mice show significantly reduced Nurr1 protein levels in the substantia nigra (SN), they display a normal range of tyrosine hydroxylase-positive neuron numbers in the SN and normal levels of dopamine in the striatum. The reduction in Nurr1 expression in Nurr1+/- mice, however, confers increased vulnerability to the selective dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) compared with wild-type (Nurr1+/+) mice. This study suggests that Nurr1 may play an important role in maintaining mature mesencephalic dopaminergic neuron function and that a defect in Nurr1 may increase susceptibility to SN injury.

L2 ANSWER 32 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 10
AN 1999:424368 BIOSIS <<LOGINID::20070510>>
DN PREV199900424368
TI Differential expression of tyrosine hydroxylase in catecholaminergic neurons of neonatal wild-type and Nurr1-deficient mice.
AU Baffi, J. S.; Palkovits, M.; Castillo, S. O.; Mezey, E.; Nikodem, V. M. [Reprint author]
CS GBB/NIDDK/NIH, 10 Center Drive, Building 10, Room 8N317, Bethesda, MD, 20892-1766, USA
SO Neuroscience, (July 15, 1999) Vol. 93, No. 2, pp. 631-642. print.
CODEN: NRSCDN. ISSN: 0306-4522.
DT Article
LA English
ED Entered STN: 18 Oct 1999
Last Updated on STN: 18 Oct 1999
AB The orphan nuclear receptor Nurr1 is a transcription factor that belongs to the steroid/thyroid hormone receptor superfamily and is expressed in many regions of the brain. To determine the physiological role of Nurr1, we previously generated mice with a null ***mutation*** in the ***Nurr1*** gene. Nurr1-null mice appear to develop normally but die within 12 h after birth. Subsequent analysis revealed the absence of neurotransmitter dopamine and tyrosine hydroxylase immunoreactivity in the central dopaminergic area of newborn pups. Herein, using in situ hybridization histochemistry, we show that Nurr1 is expressed only in subset of catecholamine producing neurons (A2 partly, A8-A10 and A11 catecholaminergic cell groups), and is excluded from the norepinephrine producing neurons (A1, A2, A5-A6 catecholaminergic cell groups). Nurr1 was not expressed in the dopamine synthesizing cell groups (A12-A16 catecholaminergic cell groups) of the diencephalon and the olfactory bulb. As previously shown and confirmed in this study, tyrosine hydroxylase immunoreactivity was absent in the substantia nigra and ventral tegmental area of Nurr1-deficient mice. However, the loss of Nurr1 expression in A2 and A11 dopaminergic neurons did not affect their tyrosine hydroxylase immunoreactivity. This study begins to dissect cues necessary for understanding the complex regulation of the catecholaminergic biosynthetic pathway with regard to local, chemical and developmental changes in the brain.

L2 ANSWER 33 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 11
AN 1998:306777 BIOSIS <<LOGINID::20070510>>
DN PREV199800306777
TI Dopamine biosynthesis is selectively abolished in substantia nigra/ventral tegmental tegmental area but not in hypothalamic neurons in mice with targeted disruption of the Nurr1 gene.
AU Castillo, Susan O. [Reprint author]; Baffi, Judit S.; Palkovits, Miklos; Goldstein, David S.; Kopin, Irwin J.; Witta, Jassir [Reprint author]; Magnuson, Mark A.; Nikodem, Vera M. [Reprint author]
CS Natl. Inst. Diabetes Dig. Kidney Dis., Natl. Inst. Health, 10/8N317, 10 Center Drive, MSC 1766, Bethesda, MD 20892-1766, USA
SO Molecular and Cellular Neuroscience, (May, 1998) Vol. 11, No. 1-2, pp. 36-46. print.
CODEN: MOCNED. ISSN: 1044-7431.
DT Article
LA English
ED Entered STN: 15 Jul 1998
Last Updated on STN: 15 Jul 1998
AB To ascertain the function of an orphan nuclear receptor Nurr1, a transcription factor belonging to a large gene family that includes receptors for steroids, retinoids, and thyroid hormone, we generated Nurr1-null mice by homologous recombination. Mice, heterozygous for a single ***mutated*** ***Nurr1*** allele, appear normal, whereas mice homozygous for the null allele die within 24 h after birth. Dopamine (DA) was absent in the substantia nigra (SN) and ventral tegmental area (VTA) of Nurr1-null mice, consistent with absent tyrosine hydroxylase (TH), L-aromatic amino acid decarboxylase, and other DA neuron markers. TH immunoreactivity and mRNA expression in hypothalamic, olfactory, and lower brain stem regions were unaffected. L-Dihydroxyphenylalanine treatments, whether given to the pregnant dams or to the newborns, failed to rescue the Nurr1-null mice. We were unable to discern differences between null and wild-type mice in the cellularity, presence of neurons, or axonal projections to the SN and VTA. These findings provide evidence

for a new mechanism of DA depletion in vivo and suggest a unique role for Nurr1 in fetal development and/or postnatal survival.

L2 ANSWER 34 OF 35 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN DUPLICATE 12
AN 1997:85809 BIOSIS <<LOGINID::20070510>>
DN PREV199799377522
TI Neuroendocrine regulation of the hypothalamic pituitary adrenal axis by the nurr1/nur77 subfamily of nuclear receptors.
AU Murphy, Evelyn P.; Conneely, Orla M. [Reprint author]
CS Dep. Cell Biol., Baylor Coll. Med., One Baylor Plaza, Houston, TX 77030, USA
SO Molecular Endocrinology, (1997) Vol. 11, No. 1, pp. 39-47.
CODEN: MOENEN. ISSN: 0888-8809.
DT Article
LA English
ED Entered STN: 26 Feb 1997
Last Updated on STN: 26 Feb 1997
AB The present study was designed to examine the role of the nurr1/nur77 subfamily of nuclear receptor transcription factors in the regulation of the hypothalamic/pituitary/adrenal axis at the neuroendocrine level. We demonstrate that this nuclear receptor subfamily can regulate the expression of the CRF and POMC genes by interacting with a specific cis-acting sequence in their proximal promoter regions. To examine the physiological significance of this response, we have focused on the POMC gene. We provide evidence that nurr1 and nur77 are rapidly induced by CRF in primary pituitary cells and that this induction is mimicked by forskolin in an anterior pituitary cell line. Further, we demonstrate that both nurr1 - and forskolin-dependent induction of a POMC-chloramphenicol acetyltransferase reporter gene are inhibited by ***mutation*** of the ***nurr1*** -binding site within the POMC promoter and that this site alone can confer cAMP responsiveness to a heterologous promoter. Finally, we provide evidence that the nurr1/nur77 response sequence is pivotal to both nurr1/nur77-dependent positive regulation and glucocorticoid receptor-dependent negative regulation of the POMC gene. These data strongly support the conclusion that the nurr1/nur77 subfamily plays an important coordinate neuroendocrine-regulatory role at all levels of the hypothalamic/pituitary/adrenal axis.

L2 ANSWER 35 OF 35 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1996:253530 CAPLUS <<LOGINID::20070510>>
DN 124:314992
TI Inhibition of Nur77/Nurr1 leads to inefficient clonal deletion of self-reactive T cells
AU Zhou, Tong; Cheng, Jianhua; Yang, Pingar; Wang, Zheng; Liu, Changdan; Su, Xiao; Bluethmann, Horst; Mountz, John D.
CS Dep. Med., Univ. Alabama, Birmingham, AL, 35294, USA
SO Journal of Experimental Medicine (1996), 183(4), 1879-92
CODEN: JEMEAV; ISSN: 0022-1007
PB Rockefeller University Press
DT Journal
LA English
AB The Nur77/Nurr1 family of DNA binding proteins has been reported to be required for the signal transduction of CD3/T cell receptor (TCR)-mediated apoptosis in T cell hybridomas. To det. the role of this family of DNA-binding proteins in thymic clonal deletion, transgenic (Tg) mice bearing a dominant neg. mutation were produced. The transgene consisted of a truncated Nur77 (.DELTA.Nur77) gene encoding the DNA-binding domain of Nur77 ligated to a TCR-.beta. enhancer resulting in early expression in thymocytes. Apoptosis of CD4+CD8+ thymocytes mediated by CD3/TCR signaling was greatly inhibited in the .DELTA.Nur77 Tg mice, compared with non-Tg littermates, after treatment with anti-CD3 or anti-TCR antibody in vivo and in vitro. Clonal deletion of self-reactive T cells was investigated in .DELTA.Nur77-Db/HY TCR-.alpha./.beta. double Tg mice. There was a 5-fold increase in the total no. Tg male mice. Deficient clonal deletion of self-reactive thymocytes was demonstrated by a 10-fold increase in the CD4+CD8+ thymocytes that expressed Tg TCR-.alpha./.beta.. There was an 8-fold increase in CD8+, Db/HY TCR-.alpha./.beta. T cells in the lymph nodes (LN) of .DELTA.Nur77 Dab/HY TCR-.alpha./.beta. double Tg compared with Db/HY TCR-.alpha./.beta. Tg male mice. In spite of defective clonal deletion, the T cell expressing the Tg TCR were functionally anergic. In vivo anal. revealed increased activation and apoptosis of T cells assocd. with increased expression of Fas and Fas ligand in LN of .DELTA.Nur77 Dab/HY TCR .alpha./.beta. double Tg male mice. Thus, inhibition of Nur77/Nurr1 DNA binding in T cells leads to inefficient thymic clonal deletion, but T cell tolerance is maintained by Fas-dependent clonal deletion in LN and spleen.

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